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## ORIGINAL ARTICLES.

### ACETYL-β-METHYLCHOLIN.

### I. THE ACTION ON NORMAL PERSONS.

### WITH A NOTE ON THE ACTION OF THE ETHYL ETHER OF β-METHYLCHOLIN.

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**Introduction.** In a recent study conducted in this laboratory, André Simonart[1] made a survey of the physiologic actions of a number of compounds of cholin, some of them new, synthesized for him by R. T. Major and his colleagues[2] in the Laboratories of Pure Research of Merck and Company. The work was undertaken because the cholin group contains a number of highly active compounds and because of the unique interest which one of these, acetyl cholin, has come to possess. First discovered as a product of artificial synthesis, acetyl cholin was later found to be present in ergot and more recently, in fresh animal tissue. Its physiologic

activity is very great, being of an order similar to that of adrenalin or histamin. Among its conspicuous actions are inhibition of the heart and increase in intestinal movement. Dale[3] has shown that there are good reasons for believing that when the vagus nerve to the heart and intestines is stimulated, acetyl cholin is released in the corresponding muscle cells and that the response induced is actually effected by the action of this chemical substance. With respect to these aspects of its action, therefore, acetyl cholin may be regarded as a chemical intermediary between parasympathetic nerve stimulation and muscular response.

The two features in the action mentioned above are among those designated as "muscarin-action" or parasympathetic action. Both are abolished by atropin. Another feature of the action, also abolished by atropin, is even more conspicuous, viz.: its power to cause dilatation of small arterioles and hence to lower blood pressure. This dilator effect is exerted not only upon vessels which possess parasympathetic innervation (*e. g.*, the submaxillary gland) but also upon those which do not (*e. g.*, vessels of the limbs). But Dale has pointed out that in these instances also there is ground for believing that stimulation of their dilator nerves (chorda tympani and posterior root fibers) is followed by the release of a chemical substance which is responsible for the consequent vasodilatation, and that this substance is acetyl cholin. If his views, based on an impressive mass of evidence,* are accepted we are obliged to regard acetyl cholin as an endogenous pharmacologic agent, released at need within the body, for the purpose of mediating highly important circulatory and gastro-intestinal reactions to nerve stimulation.

A third aspect of the action of acetyl cholin is commonly referred to as its "nicotin-action." Less conspicuous than the others, its most important feature is seen when acetyl cholin is injected intravenously into an animal after a preliminary dose of atropin. A marked rise of blood pressure ensues due to stimulation of sympathetic ganglia. When small doses are given without atropin this effect does not appear, being masked by the predominant peripheral dilator action.

Acetyl cholin is rapidly hydrolyzed in blood with the production of the far less active cholin. In consequence, no action results from oral administration; only slight and inconstant effects follow subcutaneous injection, and the actions of which we have spoken above, elicited by intravenous injection, are exceedingly evanescent. Knowledge of this instability and of its comparative ineffectiveness when given to normal man supply reasons for doubting its usefulness in human medicine.[4]

Other compounds of cholin are known which possess in different degrees the physiologic characteristics of acetyl cholin. It seemed

* The voluminous literature concerning cholin and acetyl cholin has been reviewed in Dale's Croonian lecture[3] and the references to it may be obtained from this.

not unreasonable to expect that some of these or others yet to be made might be less readily hydrolyzed, might exhibit accentuated parasympathetic effects in relation to the nicotin effects, and hence might possess greater promise as drugs potentially useful in the treatment of disorders characterized by diminished parasympathetic or by excessive sympathetic tone. Simonart's work was based upon this thought and unique opportunity for testing it was afforded by collaboration with Major and his colleagues who shortly before had discovered new chemical methods for synthesizing cholin compounds.

Two substances were encountered which, partially at least, realize the expectations with which the work was begun. These are acetyl-β-methylcholin chlorid $(CH_3)_3N(Cl)\ CH_2CH(CH_3)\ COOCH_3$, and β-methylcholin chlorid ethyl ether $(CH_3)_3N(Cl)\ CH_2CH(CH_3)\text{-}OC_2H_5$. Their actions have therefore been subjected to more detailed study than Simonart was able to give them, both in animals[5] and in man, and the former has been used with encouraging results in the clinic. The present paper deals with effects produced in normal men. In a second, a study of the gastro-intestinal action in normal and diseased conditions will be presented. Experience with the drugs in the treatment of cardiovascular disease forms the subject of a third communication and a general resumé of the therapeutic possibilities has been appended to this.†

**I. Action on Normal Persons. Acetyl-β-Methylcholin.** A brief description of the actions of this substance in animals was published by Reid Hunt[6] in 1914. Simonart's results do not agree with his and reasons were found for believing that the material used by Hunt consisted of mixtures of derivatives of α and β methylcholins. According to Simonart acetyl-β-methylcholin chlorid is much less readily hydrolyzed by blood than is acetyl cholin,[7] possesses marked muscarin and peripheral vasodilator actions and exhibits little if any of the nicotin action of acetyl cholin.[1] More detailed study of its effects in animals has been made by Comroe and Starr.[5]

Crystals of acetyl-β-methylcholin chlorid are so hygroscopic that the substance cannot conveniently be given in any dry form. It is freely soluble in water and its watery solutions do not deteriorate on standing and are relatively stable to heat. They have a bitter taste. For subcutaneous administration we have used a solution containing 20 mg. to the cc., sterilized by boiling. This caused no discomfort at the site of injection.

*Effects After Subcutaneous Injection.* Twenty healthy medical students served as volunteer subjects. The routine observations were made by ourselves or by students supervised by one of us. Each subject lay on a couch during the time of the experiment; this included a preliminary control period of 15 minutes or longer. Dosages ranged from 2.5 to 25 mg.

† We are indebted to Merck & Co. for supplying the cholin compounds used in these investigations.

A typical effect after a dose of 20 mg. is shown in Fig. 1 and the signs and symptoms occurring after the various doses are summarized in Table 1. The action appeared within a minute after the injection. Flushing of the face and neck, generalized sweating, salivation, slight fall of blood pressure, increased depth of respiration during this fall, and increase in pulse rate were almost constant features. The effect on blood pressure passed off within a few minutes. The rapid pulse rate was also transient and was often

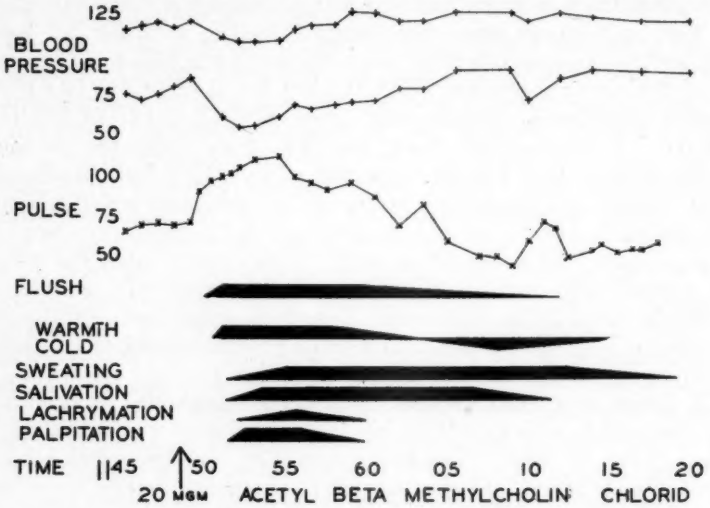


FIG. 1—Action after subcutaneous injection.

followed by a rate slower than that present in the control period. The other effects persisted for several minutes longer. The subjects, who felt warm during the flush, complained of chilliness after it had disappeared, They were glad to continue to lie down until complete recovery was attained in 15 or 20 minutes.

We listened to the hearts of many subjects during the action of of the drug. When the heart rate was slowed sinus arrhythmia appeared in most of the cases. It disappeared as the action of the drug passed off. No other type of cardiac arrhythmia was encountered. Nothing else of importance was heard. One subject was connected to the electrocardiograph (Lead II) and records were made at frequent intervals before and during the action of the drug. Besides the effect on the heart rate no significant changes were demonstrated.

We obtained no evidence of dilatation of the vessels of the extremities after subcutaneous administration. The flush was confined to the area of the emotional blush. The right foot of two subjects was placed in a Stewart calorimeter.[8] No increase in the output of heat by the foot was detected during the action of the drug.

The action on the secretion of sweat and saliva was very pronounced. In most subjects the underclothing became dampened. Salivation was also very marked. One subject who before the injection could expectorate only 0.5 cc. of saliva per minute, expectorated 4 cc. per minute during the drug's action.

TABLE 1.—EFFECT OF THE ADMINISTRATION OF ACETYL-β-METHYLCHOLIN SUBCUTANEOUSLY AND BY MOUTH TO NORMAL PERSONS.

| | Subcutaneous dosage. | | | Dosage by mouth. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5–9 mg. | 10–19 mg. | 20–29 mg. | 50–80 mg. | 100 mg. | 200 mg. | 300 mg. | 400 mg. | 500 mg. | 1000 mg. |
| No. of cases in each group | 8 | 5 | 7 | 5 | 5 | 5 | 4 | 1 | 1 | 6 |
| No. of cases showing effects given below | | | | | | | | | | |
| Systolic B. P. mm. Hg. | | | | | | | | | | |
| No change | 3 | .. | .. | 1 | 1 | .. | .. | .. | .. | 2 |
| Fall less than 10 | .. | 1 | 2 | 1 | 2 | 1 | 1 | .. | .. | 1 |
| Fall 10–20 | 3 | 4 | 3 | 3 | 1 | 2 | 2 | 1 | 1 | 1 |
| Fall more than 20 | 1 | .. | 1 | .. | .. | 1 | 1 | .. | .. | 1 |
| Rise | 1 | .. | 1 | .. | 1 | 1 | .. | .. | .. | 1 |
| Pulse rate per min. | | | | | | | | | | |
| No change | .. | .. | .. | 1 | 3 | 2 | .. | .. | .. | 2 |
| Increase less than 10 | 1 | .. | .. | .. | 1 | .. | 1 | .. | .. | 1 |
| Increase 10–20 | 1 | 1 | | | | | | | | |
| Increase more than 20 | 6 | 5 | 7 | | | | | | | |
| Decrease under 10 | 1 | 1 | 2 | 2 | .. | 3 | 1 | | | |
| Decrease 10–20 | .. | .. | .. | 2 | 1 | .. | 3 | 1 | .. | 3 |
| Flush | 8 | 5 | 7 | 1 | .. | 2 | 2 | .. | .. | 5 |
| Early sensation of warmth | 6 | 5 | 7 | .. | .. | 2 | 1 | .. | .. | 3 |
| Later sensation of cold | 3 | 1 | 3 | .. | .. | .. | .. | .. | .. | 1 |
| Sweating | 5 | 5 | 7 | 2 | 1 | 1 | 1 | .. | 1 | 4 |
| Salivation | 5 | 5 | 7 | 1 | 1 | .. | .. | .. | 1 | 2 |
| Lachrymation | 3 | 2 | 3 | | | | | | | |
| Increased peristalsis | 2 | .. | 2 | 1 | .. | 1 | .. | .. | 1 | 5 |
| Epigastric discomfort | .. | .. | 1 | 1 | 2 | 2 | .. | 1 | .. | 2 |
| Constriction under sternum | 1 | .. | 1 | | | | | | | |
| Palpitation | 8 | 5 | 7 | | | | | | | |
| Increased respiration | 8 | 5 | 7 | | | | | | | |

Aside from the transient increase in depth of breathing no effects of the drug on the respiratory system could be demonstrated in the majority of our subjects. We listened to the chests of 5 subjects but could not detect râles in any. Three others coughed a few times.

One subject had a typical asthmatic attack immediately following the administration of the drug. It lasted for about 3 minutes and then subsided spontaneously. This was the only reaction to the drug which could be considered at all alarming. The subject gave a history of having had asthma before, and the attack can be attributed to the bronchoconstrictor action of the drug, which has been demonstrated in animal experiments.[5] Three other subjects reported a sensation of "pressure" or "constriction" under the sternum, and one referred this sensation to the precordium. The cause of these sensations may only be surmised; perhaps they should be attributed to bronchoconstriction.

Gastro-intestinal effects were demonstrated in only a few subjects. We listened for peristalsis in 5 subjects before and after

the administration of the drug. An increase in frequency and intensity of the sounds was very obvious in 2; in the others this was not obvious, possibly because peristalsis was very active before the drug was given. Four others reported that they had increased bowel movements during the subsequent 6 hours. One of these had 3 liquid stools. One subject reported slight nausea after the injection; it passed off quickly.

In 2 subjects we were unable to demonstrate any effect on either the basal metabolic rate, the respiratory quotient, or the blood sugar after injections of 5 and 15 mg.

*The Action After Administration by Mouth.* The promptness and severity of the symptoms which followed the subcutaneous administration of acetyl-β-methylcholin chlorid stand in sharp contrast with the slow onset and mildness of the action after giving the drug by mouth. The dosage required to produce noteworthy effect by mouth was between 50 and 100 times as large as the subcutaneous dosage. Even after the largest doses the effects came on so gradually that the subject was usually entirely unaware that the drug was acting.

The action after administration by mouth has been studied in 27 subjects, 14 of whom were normal medical students or members of the staff, the remainder being hospital patients who were essentially normal. The majority of the observations were made on subjects who remained lying down for the whole morning. A few continued to perform their duties around the hospital ward and sat in a chair for 10 minutes prior to the taking of observations.

A summary of the effects detected after various doses of acetyl-β-methylcholin chlorid is given in Table 1. The initial effects were noted from 15 to 75 minutes after the administration of the drug. The duration of the symptoms depended on the dosage. After small doses they usually continued for ½ to 1 hour; after the largest doses they lasted much longer, for 3 hours in 1 subject. The typical effects were a fall in blood pressure, the diastolic often falling farther than the systolic, and a diminished pulse rate. After small doses the other symptoms which occurred so regularly after subcutaneous injections were usually absent, after large doses they usually appeared as shown in Table 1.

The gastro-intestinal action usually exceeded that demonstrated after subcutaneous injection. Increased peristalsis was regularly noticed by the subjects and audible to the observer after doses of 1 gm. Defecation did not always follow because in 5 of the 6 subjects taking this dose the action was cut short by atropin. The 1 given no atropin had 3 bowel movements. Another subject had the same number after taking 50 mg.; 2 others had single stools.

Eight of the subjects complained of slight epigastric discomfort immediately after taking the drug, long before any other action was demonstrable. This was not true nausea and there was no

fear of vomiting. We later learned that this could usually be avoided by giving the drug in milk, so the discomfort is to be attributed to local irritation.

As the flush, so obvious in the face and neck, could not be seen elsewhere, 5 experiments were made to determine whether any vasodilatation occurred in the feet. The subjects lay on a couch with their feet bare. Thermal junctions were fastened to the dorsum of each second toe by wide strips of adhesive, and the skin temperature was determined at frequent intervals before and during the action of 1 gm. acetyl-β-methylcholin chlorid, given by mouth, and after 0.6 mg. of atropin sulphate had been given subcutaneously to antagonize its action. During the control period the skin temperature always diminished steadily toward that of the room air. In 3 instances, when the other symptoms of the drug's action commenced, the skin temperature stopped falling and began to rise. In 1 case the increase amounted to 4° C and was accompanied by some reddening, in the other 2 it was much less, 0.7° C., and no change of color was detected. As the room temperature did not change, the blood pressure did not rise and sweating increased during the drug's action, the increased skin temperature may be interpreted as indicating vasodilatation. This effect was halted by atropin in 2 of the 3 subjects. In 2 subjects no evidence of a vasodilator action on the feet was secured.

In 2 subjects (S. and C.) the effects of the drug on respiration and cardiac output were studied by means of the method of Starr and Gamble.[9] The subjects had had no food for 15 hours and they rested 1¼ hours before the first estimation and remained lying down throughout the determinations. Duplicate estimations were made before the drug was administered, a second pair after characteristic changes in blood pressure and pulse rate had taken place, a third pair after the action had been antagonized by atropin. Dosages of 200 and 400 mg. produced no noteworthy change in respiration or cardiac output in these cases, nor did any change follow the administration of atropin.

In these same experiments the metabolism was estimated from samples of expired air taken from the mixing bottle; in 2 other subjects it was determined by the Benedict-Roth apparatus. We are indebted to Dr. Robert Shaw for the analyses of the samples. In 2 instances the metabolism was unaltered; in 2 others it fell considerably. As 1 of the latter subjects had shown no metabolic change after a subcutaneous injection, the diminution is not to be attributed to the drug.

An electrocardiogram was taken after a dose of 100 mg. by mouth had caused a slowing of the heart rate to less than 60 a minute. It demonstrated a simple bradycardia with sinus arrhythmia. Another electrocardiogram taken on the same subject after the effect of the drug had passed off did not show sinus arrhythmia.

One subject, a strong and vigorous man, took a gram of the drug 4 times a day for 2 periods totaling 35 days. During the first few days of each period the laxative action was marked; the patient's stools increasing from 1 to 3 or 4 daily. This continued for several days and then the number of stools slowly diminished to normal, though the drug was continued. Salivation was noted at irregular intervals occurring 15 to 25 minutes following the taking of the drug. Increased sweating was not observed by the patient, but the test was conducted in mid-summer and some sweating was usually present. The night and morning pulse rates were not significantly different during the administration of the drug from those obtained before and afterward. The blood pressure was irregular during the control periods and there was no noteworthy change during the action of the drug. The subject had no discomfort at any time.

*Other Methods of Administration.* The intramuscular injection of acetyl-β-methylcholin chlorid into 2 normal medical students produced effects which seemed identical with those obtained after subcutaneous administration. When a solution of the drug was sprayed on the mucous membrane of the nose a definite flush of the face was observed in 2 cases.

Intravenous administration has not been attempted in man. The rapidity and vigor of the effects following subcutaneous administration indicate that the action following intravenous injection would be very severe. Judging from animal experiments, prolonged cardiac arrest would follow an overdose.

*Comparison with and Relation to the Action of Other Drugs.* The power of atropin to abolish the action of acetyl-β-methylcholin chlorid was demonstrated many times on our subjects. If 0.6 mg. of atropin sulphate was given subcutaneously an hour before an injection of the acetyl-β-methylcholin chlorid the latter had practically no effect, very transient flushing being the only thing observed. When this dose of atropin was given in the same solution as the acetyl-β-methylcholin chlorid, the action of the latter appeared with the usual intensity, but its duration was considerably shortened. If the same dose of atropin was injected when the action of a previous injection of acetyl-β-methylcholin chlorid was at its height, it caused a material shortening of the duration of the action.

It is of interest to compare the action of acetyl-β-methylcholin chlorid with that of acetyl cholin. The latter drug was injected subcutaneously in doses of 50, 70 and 100 mg. into 6 subjects, who also received acetyl-β-methylcholin chlorid. Acetyl cholin had very little effect even in the largest dosage, the blood pressure and pulse rate rising a little, but not more than is likely to occur from apprehension in this type of experiment. Several subjects objected to the pain caused at the site of injection. In 2 slight transient flushing occurred. We regard this as the only definite evidence we

obtained that this drug was acting at all. The effect was much less than that regularly obtained after a subcutaneous dose of 5 mg. of acetyl-β-methylcholin chlorid. Therefore, there can be no doubt that acetyl-β-methylcholin chlorid is a much more powerful and more dependable drug than acetyl cholin when administered subcutaneously in man. Even after intravenous injection the action of acetyl cholin seems too transient for therapeutic usefulness.[4]

THE ETHYL ETHER OF β-METHYLCHOLIN. The ethers of cholin are more stable than the esters, and so they might be superior for oral administration. This afforded the reason for making some preliminary experiments on the action of the ethyl ether of β-methylcholin chlorid which is known to be more stable in body fluids[7] than acetyl-β-methylcholin chlorid although it is somewhat less active.[5]

Subcutaneous doses of 10 or 20 mg. of this drug given in aqueous solution (1 cc. = 20 mg.) to 5 normal persons produced effects similar to those described for the same doses of acetyl-β-methylcholin chlorid except that the action on blood pressure and pulse rate was less marked, while that on the secretion of sweat and saliva was of longer duration than the effects obtained after acetyl-β-methylcholin chlorid.

When given by mouth the effective dose of the ethyl ether of β-methylcholin chlorid was found to be considerably smaller than that of acetyl-β-methylcholin chlorid, ranging from 20 to 100 mg. It has been given to 10 normal persons. The typical response to such dosage was very marked sweating and very marked salivation, which lasted from 30 to 90 minutes. There was comparatively little change of pulse rate or blood pressure. However, the circulatory effects, as flush, diminution of blood pressure and pulse rate, were observed in some cases. The laxative action was seen in 2 cases. It, therefore, appears that the ethyl ether of β-methylcholin chlorid is the better drug for the production of sweating or to increase the flow of saliva, but if effects on the cardiovascular system are desired, acetyl-β-methylcholin chlorid is superior.

**Summary and Discussion.** In experiments on 47 normal persons, acetyl-β-methylcholin chlorid has proved to be a drug which, when injected subcutaneously in suitable dosage, exerts a prompt and vigorous action. A fall in blood pressure, a rise of pulse rate, flushing, sweating and salivation are the outstanding effects. The acute phase of this action comes on within a minute or 2 after injection and lasts for 2 or 3 minutes. All evidence of action passes away in 15 or 20 minutes. The only untoward effect encountered was the production of a transient attack of asthma in a subject who had previously suffered from this condition.

Given by mouth, acetyl-β-methylcholin chlorid has a much milder effect than that following subcutaneous injections. Given by the former method, even in very large doses, it does not cause discom-

fort, although considerable blood pressure and pulse rate changes have been noted. The dosage required to produce effects by mouth is so much larger than the subcutaneous that the destruction of large amounts of the drug in the gastro-intestinal tract seems probable.

The ethyl ether of β-methylcholin given by mouth or subcutaneously has less effect on the cardiovascular and gastro-intestinal systems, but more effect on the salivary and sweat glands than acetyl-β-methylcholin chlorid. Therefore, the latter seems preferable in all cases except where sweating and salivation are especially desired. That the ethyl ether of β-methylcholin chlorid is a vigorous diaphoretic without many untoward side effects is undoubted.

Most of the effects of these drugs demonstrated in man are similar to those obtained in animal experiments.[1,5] They are analogous to those which follow stimulation of the parasympathetic nerves accompanied by peripheral vasodilatation. An exception to this statement is the increase of pulse rate which occurred so regularly in our subjects after a subcutaneous injection of the drug. Light is thrown on this apparent contradiction by a number of observations. In a few subjects, after large doses of the drug, we have demonstrated a sharp fall in pulse rate before the flush began and the blood pressure diminished. This fall lasted only a few seconds and was then succeeded by the characteristic rise. In many subjects, as illustrated in Fig. 1, after the acute phase of the action was over, the pulse rate diminished until it was slower than before the drug was administered. In 1 case, during this period of slowing, a subcutaneous injection of atropin sulphate in sufficient dosage to abolish the action of acetyl-β-methylcholin chlorid was followed by an increase of 10 beats per minute. This indicated that the slowing was due to the drug. As this decrease of heart rate occurred before and after, but not during the period of diminished blood pressure, it seems likely that the compensatory mechanisms which are called forth by any sharp fall of blood pressure, caused the heart to break away from the vagus inhibition. After administration by mouth the blood pressure falls so slowly that this type of compensation is not needed, and slowing of the pulse is the usual finding.

It is of interest to compare the action of acetyl-β-methylcholin chlorid with that of acetyl cholin in our normal subjects. In animal experiments an intravenous injection of acetyl-β-methylcholin chlorid has effects on the cardiovascular system essentially similar to those which follow acetyl cholin.[1] But judging by the effects which follow subcutaneous injections into normal men, acetyl-β-methylcholin chlorid is over 10 times as powerful. It can also be given by mouth whereas acetyl cholin is ineffective when thus administered. It also lacks certain of the undesirable side effects of acetyl cholin. Therefore, we believe that acetyl-β-methylcholin should supplant acetyl cholin in all conditions in which that drug is used for therapeutic purposes.

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## ACETYL-β-METHYLCHOLIN.

## II. THE ACTION ON THE GASTRO-INTESTINAL TRACT OF NORMAL PERSONS, IN ABDOMINAL DISTENTION, AND IN CERTAIN OTHER CONDITIONS.

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ALLUSION has been made in the first paper[1] of this series to the probability that in the normal animal stimulation of the vagus nerve to the gastro-intestinal tract is followed by increased motor activity because of the liberation in the muscle cells of the highly active chemical substance acetyl cholin. This conception was in part derived from the results of experiments conducted in Magnus' laboratory[2] which suggested that cholin was of importance in the regulation of normal gastro-intestinal motility. The instability of acetyl cholin in blood, responsible we believe for absence of action when given by mouth, and for inconstant effects when given subcutaneously, makes it of little importance as a drug. When it was discovered that acetyl-β-methylcholin is more stable than acetyl cholin,[1,3,4] that it possesses similar parasympathetic actions, that in animal experiments it is highly effective in increasing the contractions of gastro-intestinal muscle and that it frequently exhibits laxative action when given to normal men, it became apparent that its possibilities as a useful drug should be studied in the gastro-intestinal clinic. The results of such a study are reported in this paper.

METHODS. *Gastric Secretion.* For study of the effect of the drug on gastric acidity, the entire contents were withdrawn as completely as possible at intervals varying from 5 to 20 minutes through a small stomach tube. Ten cc. of each specimen were used for analysis; the rest was returned to the stomach. Acidity was determined by titration with N/50 NaOH, using dimethylaminoazobenzene and phenolphthalein as indicators.

*Gastric Tone and Peristalsis.* The subjects swallowed a rubber balloon attached to a stomach tube. The balloon was then filled with 100 cc. of water and the tube connected with a tambour for recording gastric contractions. A levelling bulb was used for keeping the pressure on the contents of the balloon constant at about 15 cm. of water (Fig. 1). This procedure was frequently carried on coincidently with the colonic studies noted below.

*Tone and Peristalsis of the Jejunum* were similarly recorded by the use of a smaller balloon carried into the jejunum by normal peristalsis. It was filled with 30 cc. of water, and its position was determined by the fluoroscope.

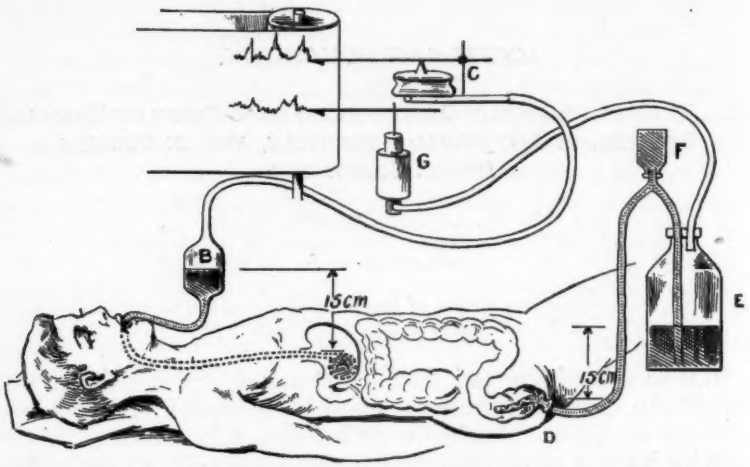


FIG. 1.—Technique of recording gastric and colonic activity. *A*, water-filled intragastric balloon containing 100 cc.; *B*, levelling bulb for excess balloon fluid maintaining hydrostatic pressure of not more than 15 cm.; *C*, recording tambour; *D*, rectal tube; *E*, bottle containing 2 liters of warm isotonic sodium sulphate with fluid level not more than 15 cm. above rectum; *F*, trap to withdraw flatus from syphon system; *G*, volume recorder.

*Colonic Tone and Movement* were measured and recorded by the apparatus represented in Fig. 1. The patients were prepared by 12 hours of fasting, a mild laxative the evening before, and a plain water enema at least 3 hours before the test. The colon was filled with isotonic sodium sulphate solution introduced through a siphon-tube leading from a reservoir adjusted to maintain a pressure of about 15 cm. of water. A tambour connected with the reservoir recorded movement of fluid into or out of the colon consequent upon changes in its tone or motility. Sodium sulphate solution was chosen because of its slight absorbability.

*Roentgen Ray Observations* were made by means of the usual barium meal or enema. In 1 instance the barium was introduced directly into the duodenum through a tube. For these observations I am indebted to Doctors E. P. Pendergrass, K. Kornblum and M. L. Allen.

RESULTS. When given subcutaneously the drug always produced the effects described by Starr, Elsom and Reisinger,[1] namely, flushing, sweating, salivation, fall of blood pressure, transient increase in pulse rate. When it was given by mouth these effects were so slight as to be detectable only by careful observation.

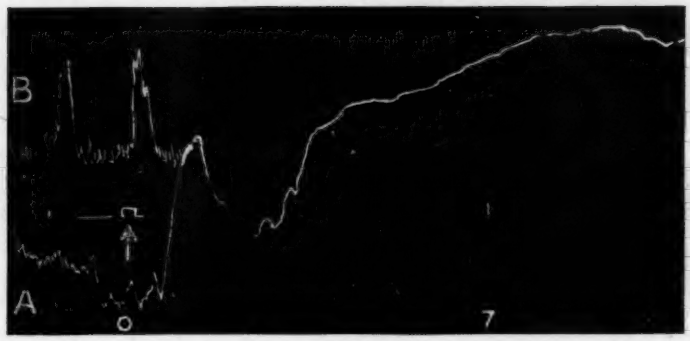


FIG. 2.—*A*, colonic tracing; *B*, gastric tracing (Fig. 1). Stomach empty for 12 hours previously. Given acetyl-β-methylcholin, 17 mg., subcutaneously. Colonic tone increased within 2 minutes, reaching a maximum in 8. Hunger contractions previously regular were abolished without alteration of tone.

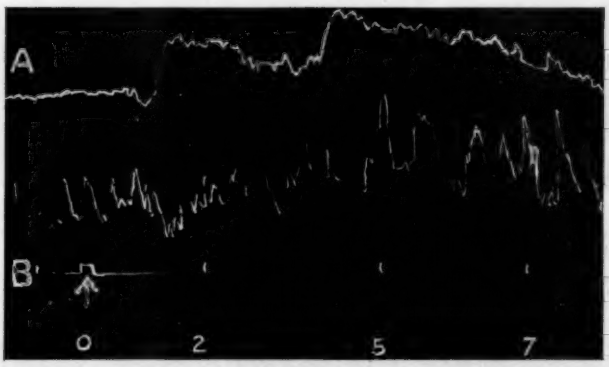


FIG. 3.—*A*, colonic tracing; *B*, gastric tracing presumably from the antrum (Fig. 1). Patient ate a full meal 2 hours before the experiment. Given acetyl-β-methylcholin, 10 mg., subcutaneously with increase in both colonic and gastric tone and peristalsis. Maximum effect approximately 5 minutes after injection, coincident with the subsidence of the prompter cardiovascular reaction.

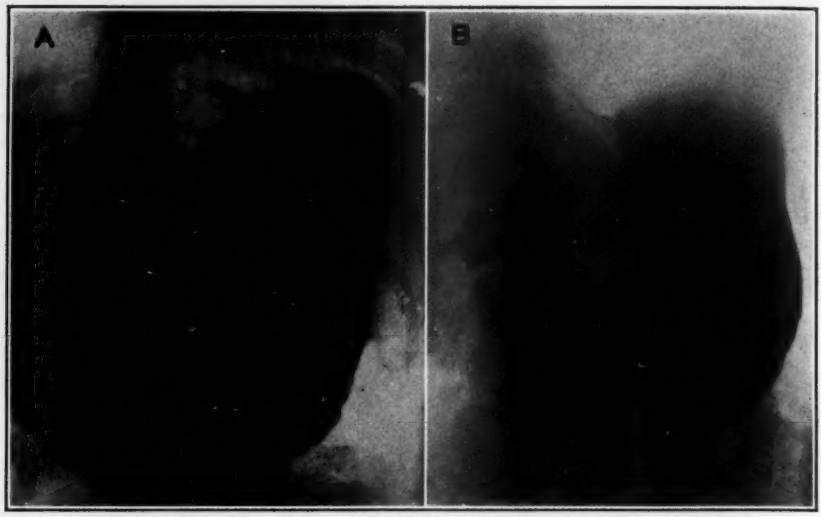


FIG. 4.—Roentgenograms of stomach. Ten milligrams of acetyl-β-methylcholin given subcutaneously. *A*, before injection stomach is somewhat relaxed with shallow peristalsis and fair motility of its contents, the duodenal "cap" being poorly filled; *B*, 5 minutes after injection gastric tone is increased, peristalsis deeper and more active forcing the gastric contents rapidly from the stomach and filling the duodenal cap.

FIG. 5.—Jejunal tracing recorded by water-filled balloon 30 cm. distal to ligament of Treitz. Acetyl-β-methylcholin, 400 mg. in 80 cc. of water, given by mouth. Marked increase in tone and peristalsis beginning within a minute. A minute perforation of the balloon allowed the pointer to fall steadily, thus recording less than the actual tonus response of the intestine.

FIG. 6.—Jejunal tracing recorded as in Fig. 5, the balloon lying 35 cm. distal to ligament of Treitz. Acetyl-β-methylcholin, 15 mg., given subcutaneously. Prompt fall in tone and reduction in peristalsis during period of lowered blood pressure with subsequent marked rise in tone and increased peristaltic activity.

*Action on Gastric Secretion.* Action of acetyl-β-methylcholin on volume of gastric secretion was studied in 9 persons who showed no symptoms of gastro-intestinal disorder. The drug was tried both subcutaneously (5 to 10 mg.) and orally (200 to 300 mg.). In 2 cases, rather marked increase occurred; in 4, some increase was suggested; in none was there distinct decrease in volume. Precautions were taken against swallowing of saliva; in 8 out of the 9 trials, evidence of pyloric regurgitation was obtained by the detection of bile in the gastric contents withdrawn after the drug was administered. No marked change in acidity in these cases followed the administration of the drug. In 5 it was slightly decreased, in 1 increased, in 3, unchanged.

The drug was tested in 6 cases of hypochlorhydria. In 3 it caused a definite increase in acidity. In 2 of these, histamin gave a greater response in doses causing less systemic reaction than did acetyl-β-methylcholin. These results are recorded in Table 1. Those of previous gastric analyses obtained from the records of the hospital laboratory are recorded for comparison. Of the 3 cases in which no increase occurred, one received the drug by mouth and in another the subcutaneous dose was small (5 mg.).

TABLE 1.—EFFECT OF ACETYL-β-METHYLCHOLIN UPON GASTRIC SECRETION IN HYPOCHLORHYDRIA.

| Case. | Sex. | Age. | Diagnosis. | Duration |
|---|---|---|---|---|
| *Clinical Status:* | | | | |
| 1 | F | 37 | Renal tuberculosis | 6 mos. |
| | | | Chronic duodenal ileus | 5 yrs. |
| 2 | F | 20 | Chronic duodenal ileus | 18 mos. |
| 3 | F | 29 | Chronic bronchitis | 5 wks. |

| Case. | Date. | Stimulant in addition to gruel. | Results in free HCl. 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. |
|---|---|---|---|---|---|---|---|---|---|---|
| *Secretory Studies:* | | | | | | | | | | |
| 1 | 5/30 | 0 | 0 | 0 | 0 | 0 | 11 | 49 | | |
| | 7/32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 7/32 | H. 0.3 mg. | 0 | 0 | 0 | 0H | 14 | 26 | 32 | 3 |
| | 8/32 | A. 15.0 mg. | 0 | 0 | 0 | 0A | 10 | 10 | 18 | 14 |
| 2 | 9/31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 8/32 | H. 0.3 mg. | 10 | 0 | 0 | 0 | 0H | 0 | 0 | 16 |
| | 8/32 | A. 10.0 mg. | 0 | 0 | 0 | 0 | 0A | 9 | 12 | 13 |
| 3 | 8/32 | A. 10.0 mg. | 0 | 0 | 0 | 0A | 5 | 19 | 8 | 32 |

NOTE.—Each case received 300 cc. of oatmeal gruel immediately after the first aspiration. Letters H and A stand for histamin acid phosphate and acetyl-β-methylcholin respectively. When placed after a figure in the table they signify that a subcutaneous injection of the indicated drug was given immediately after that aspiration.

In 3 cases of achlorhydria not due to Addisonian anemia or gastric carcinoma, neither histamin nor acetyl-β-methylcholin produced detectable secretion of acid.

From these results we may conclude that while acetyl-β-methylcholin in the doses tested has little action on normal gastric secretion, it may occasionally increase the secretion of acid in patients suffering from hypochlorhydria.

*Gastric Motility.* When the stomach was empty, subcutaneous administration of 7 to 17 mg. of acetyl-β-methylcholin or oral administration of 200 to 400 mg. was followed by cessation of the normal hunger contractions (Fig. 2). This was observed in each of 10 cases. Hypodermics of sterile water or administration of water or aromatic spirits of ammonia by mouth had similar but less prolonged effect.

The effect was different if the drug was given when the stomach contained food. In 5 cases increased peristalsis and tone followed the subcutaneous injection of 10 mg. (Fig. 3). In 2 of these cases and in 3 others the same effect on peristalsis was demonstrated by fluoroscopic observation after a barium meal (Fig. 4). In 1 of these the narrowing of the gastric outline identified increased tone. In another case the fluoroscope did not exhibit increased peristalsis but the balloon gave a record of increased tone.

It is therefore evident that the action of acetyl-β-methylcholin on motility varies with the physiologic condition of the stomach; when empty, contractions are diminished; when food is present either or both tonus and peristalsis are increased.

*Action on the Small Intestine.* Kymographic records were made of the response of the small intestine in 3 fasting subjects. In 1 the drug (400 mg.) was given by mouth. Both tone and peristalsis were immediately increased (Fig. 5). In the other 2 cases, the drug was given by subcutaneous injection (15 mg.). Tone and peristalsis were increased in both. This followed a transient decrease in peristalsis in 1; in the other, a decrease in tone (Fig. 5).

Roentgen ray study of the action of acetyl-β-methylcholin on the small intestine has been made in 5 individuals. In 4 of these the drug was given after a barium meal, in 1 after direct introduction of barium into the duodenum. In every case peristalsis was increased; in 1, the narrowing of the column of intestinal contents suggested increase in tone. The increase in motility resulted in hastened advance of the intestinal contents.

The predominant effect of acetyl-β-methylcholin on the small intestine is increase of peristalsis and tone.

*Action on the Colon.* Identification of action on the colon was more difficult than on the upper gastro-intestinal tract because of the irregularity of the graphic records during the control period. In each of 6 cases, however, the subcutaneous injection of from 5 to 15 mg. of acetyl-β-methylcholin caused elevation of tone which occurred within 2 minutes and lasted from 5 to 30 minutes (Figs. 2 and 3). In 3 of these peristalsis was increased; in 1 decreased; in 2 unchanged.

In 1 case 10 mg. were given subcutaneously while the colon, filled with a barium enema, was observed through the fluoroscope. Immediate increase in propulsive movement occurred.

After oral administration, the response, if any occurred, was

delayed. In 2 cases an abrupt increase in tone occurred 30 to 40 minutes after doses of 200 and 300 mg. This is the interval which Starr, Elsom and Reisinger found to elapse between taking the drug by mouth and signs of systemic action. In 3 cases, no action on the colon could be detected during the hour following oral administration of 200 or 300 mg. In 1 subject, 300 mg. of acetyl-β-methylcholin were given every 4th hour for 2 days. A barium enema was given before administration of the drug began and again 5 hours after the last dose. Comparative fluoroscopic observations indicated that the capacity of the colon had increased.

The above results indicate that increase in tone of the colon consistently follows subcutaneous administration of acetyl-β-methylcholin and that this is sometimes associated with increased peristalsis. In only a fraction of the trials did this result follow oral administration.

*Routine Gastro-intestinal Roentgen Ray Examination.* Slight to moderate increase of gastric peristalsis was observed in all of 6 cases receiving the routine barium meal following a course of acetyl-β-methylcholin by mouth. Each case had been studied immediately before the administration of the drug which was carried out in doses of 0.25, 0.6, 0.8, 0.9, 1.2, and 3 gm. respectively per 24 hours throughout the 2 days before and 3 days occupied by the examination. The degree of effect was proportional to the dose, the barium causing some nausea and pylorospasm in the case receiving 3 gm. per day. Small intestinal activity appeared unchanged but in spite of a distinct laxative effect in the 4 cases receiving the highest dosage the general impression of the fluoroscopist was of decreased colonic activity. In cases receiving 1.5 and 3.0 gm. per day colonic stasis seemed unequivocal.

CLINICAL STUDY. The experimental observations suggest that acetyl-β-methylcholin is fundamentally a stimulant to gastro-intestinal motor activity and that with proper choice of dosage and method of administration one might count upon this taking place with fair regularity. Two conditions, constipation and post-operative distention have been used to test this effect.

*Laxative Action.* Few cases receiving 400 mg. or more of the drug by mouth have failed to note an increase in the number of their stools, though frequently smaller doses have been laxative. Movement of the bowels after subcutaneous injection occurs only occasionally. During a course of the drug frequent stools are passed during the first day or two, thereafter a decrease to 1 or 2 a day commonly occurring. Cramps have followed only so large a dose as 1 gm. by mouth.

*Use in Postoperative Distention.* In 9 of 14 cases of abdominal distention symptomatic relief followed the exhibition of the drug. This was accompanied by increase of peristaltic sounds over the abdomen, frequent expulsions of gas by rectum, and appreciable

reduction in the abdominal distention. Of the 5 cases unrelieved, 2 were observed to have increased peristaltic activity, 1 was unchanged and in 2 others observations were not made. In 1 of these, a patient of 68 years, bronchial spasm resulted with sufficient discomfort to warrant an injection of atropin which as usual abolished the effect of the acetyl-β-methylcholin promptly.

The 3 cases in which the most favorable results occurred are here reported in detail.

**Case Reports.** CASE 1.—E. C., a white male, aged 56 years, admitted for posterolateral sclerosis of Addisonian anemia, had recovered a normal blood count under liver therapy. His chief complaint, abdominal distention, had remained unabated for 2 weeks in spite of hot fomentations, turpentine stupes to the abdomen, an inlying rectal tube, repeated simple enemas, charcoal by mouth, and a nightly dose of 30 cc. of liquid petrolatum and 10 cc. of aromatic fluid extract of cascara. He was then given 200 mg. of acetyl-β-methylcholin by mouth, 3 times a day for 2 days without effect. When the dose was increased to 300 mg. the passage of flatus immediately began with complete relief of distention after the first dose. The drug was continued 3 times a day with no recurrence of symptoms for 3 days and then discontinued. Within 18 hours the distention and discomfort returned again to be controlled by the 300 mg. dosage. During the subsequent 5 months the patient has continued to get relief from doses of 300 mg. whenever distention has occurred.

CASE 2.—X. X., a white woman, aged 45 years, became markedly distended 24 hours after a laparotomy. While in considerable pain with frequent vomiting, 20 mg. of acetyl-β-methylcholin were injected subcutaneously. Immediately the abdominal pain increased, and for 10 minutes salivation and nausea were marked. Then copious expulsions of gas by bowel occurred continuing intermittently for ½ hour. At the end of this time the distention had disappeared and the patient was relieved of her symptoms.

CASE 3.—H. B., a white woman, aged 36 years, developed phlebitis 18 days after a nephrotomy which had already been complicated by a brief postoperative atelectasis. Intractable abdominal distention followed, for the relief of which turpentine stupes and asafetida enemas had been totally ineffectual. A dose of 300 mg. of acetyl-β-methylcholin was given by mouth. Nausea resulted with belching and in ½ hour the abdominal pain had markedly increased. No passage of gas occurred until a rectal tube was inserted 1 hour and 20 minutes after the administration whereupon immediate and copious expulsions occurred with relief of distention and abatement of symptoms.

**Discussion.** Motor stimulation as evidenced by increase in tone and peristalsis is the chief gastro-intestinal effect of acetyl-β-methylcholin, though secretory activity of the stomach may be at times increased. This conclusion is based upon the results of animal experimentation,[4] special studies in normal individuals,[1] and the use of the drug in the clinical conditions described. Exceptions occur in the abolition of gastric-hunger contractions where the effect is apparently carminative in type, and in the decrease in activity of the small intestine during the period of vasodilatation

which follows a subcutaneous injection. This effect of vascular hypotension upon intestinal activity has been recognized in many conditions.[5]

Apparent discrepancies appear between the results of balloon experiments on the small gut and the fluoroscopic studies after a barium meal. In the latter method the absence of objective records necessitating a comparison of activity with one's recollection of that seen 5 days previously makes the identification of small changes very difficult. In most instances 2 hours or more elapsed between the study and the next preceding dose of the drug so that if any effect occurred it may have been already passing off. At least it suggests that repeated doses will not produce a state of continuous hyperactivity of recognizable degree. In the colon apparent contradiction is again present. Subjects, in whom the fluoroscopic study revealed some stasis, reported a laxative effect. This frequent defecation, as noted above, occurred chiefly in the first 2 days of a course while 3 to 5 days usually elapsed before the colonic study was made. Constipation was absent in all the patients taking acetyl-β-methylcholin even though but 1 stool a day was passed. This result, as in the case of the small intestine, suggests that a continuous effect could not be achieved by repetition of the doses at such intervals as were used in this study.

The secretory effects of the drug on the stomach even when it has been given subcutaneously have been less clearly demonstrable than the motor. Only in hypochlorhydria has hydrochloric acid secretion been unquestionably stimulated. Even here acetyl-β-methylcholin caused more discomfort to the patient for the increase in acidity elicited than did histamin. Because of the numerous factors influencing any study of gastric secretion by clinical methods, however, these results must be looked upon as merely suggestive.

When the drug is given by mouth in sufficient dosage, gastro-intestinal motor effects follow while the side effects are minimal. This is the method of administration to be preferred when this action is desired clinically. By means of it certain cases of distention have been relieved in which laxatives, enemas and stupes have been unavailing. It therefore seems probable that this drug will find a place in the treatment of certain gastro-intestinal disorders.

In conclusion I wish to acknowledge my indebtedness to Mr. J. P. English for his technical assistance, to the Radiologic Staff of the University Hospital for their coöperation in the Roentgen ray studies and to Drs. T. McK. Downs, F. A. Bothe, R. J. Veal and C. G. Jordan for their reports upon the effects of this drug in abdominal distention.

**Summary.** 1. Acetyl-β-methylcholin, by whatever route given, affects the gastro-intestinal tract as well as the other viscera supplied by the parasympathetic system. This effect is most satis-

factorily achieved by oral administration, secretory and cardiovascular activity dominating the picture after subcutaneous injection.

2. The usual gastro-intestinal effects are an increase in tone and movement. This is not the case in the fasting stomach or in the small intestine during the period of falling pressure after subcutaneous injection.

3. Beneficial clinical effects have been manifested by slight stimulation of gastric secretion in some cases of hypochlorhydria, by a comfortable laxative effect in most individuals taking large doses by mouth, but chiefly in the relief of abdominal distention in certain instances in which the usual procedures had failed.

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## ACETYL-β-METHYLCHOLIN.

### III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, With a Discussion of Its Action in Other Conditions.

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In the investigation reported in a preceding communication[1] it was demonstrated that the subcutaneous injection of acetyl-β-methylcholin into normal persons was promptly followed by a vigorous but not dangerous type of action, the more usual manifestations of which were marked flushing, sweating, and salivation, accompanied by a fall in blood pressure and a rise of pulse rate. The acute stage of this action lasted only 2 or 3 minutes; all the symptoms passed off within 15 or 20 minutes. When given by mouth the action was mild. No uncomfortable or alarming manifestations were ever produced. A gradual fall in blood pressure and pulse rate usually took place but the other symptoms occurred with less frequency.

Pharmacologic studies have shown[2,3] that part of the action of this drug is similar to that which follows stimulation of the vagus

nerve and other parts of the parasympathetic nervous system. Therefore, it seemed proper to try to utilize this effect to benefit cases of paroxysmal tachycardia, a condition in which the attack may often be arrested by vagus stimulation. Another effect of this drug is peripheral vasodilatation, and we have sought to employ this type of action in the treatment of the spastic types of peripheral vascular disease. The purpose of this communication is to report the results of our study of the drug's action in these and certain other types of cardiovascular disease and to point out additional aspects of its action which might be useful in the treatment of other conditions. If given subcutaneously in adequate dosage the drug brings most attacks of paroxysmal tachycardia to an end immediately. Given by mouth it causes the relaxation of the arterial spasm of Raynaud's disease, provided the spasm is not too severe, and has been used with success in the symptomatic relief of certain patients suffering from this and other conditions in which vascular spasm occurs. The results obtained in other cardiovascular conditions are less striking but certain cases of headache were undoubtedly relieved.

**The Utility of the Vagus Action.** *The Effect on Paroxysmal Tachycardia.* Twenty-nine attacks of this condition in 9 patients have been treated by injections of acetyl-β-methylcholin. Electrocardiograms obtained in all but 2 patients showed the attacks to be of the auricular or supraventricular type. I am indebted to Drs. B. I. Comroe, F. W. Burge, and J. M. Hayman for a report of the results in cases M. F., W. S. (Attacks 1 and 2) and P. R. respectively. I am also indebted to Dr. F. C. Wood for making and interpreting the electrocardiograms.

In the large majority of instances an attempt was made to stop the attack by pressure on the carotid arteries high in the neck before the drug was given. This procedure, commonly known as vagus pressure, has been demonstrated by Hering[4] to produce its effect by means of a carotid sinus reflex and not by direct vagus stimulation. Therefore, it will be spoken of as carotid pressure in this paper. Twenty attacks were brought to an end by this means alone during the course of the investigation.

If carotid pressure was unsuccessful the drug was given subcutaneously. In typical cases flushing of the face and neck appeared in about a minute. A few seconds later a brief cardiac pause occurred, followed by a momentary period of irregularity of both rhythm and intensity of heart sounds and pulse, and then by normal rhythm. The blood pressure diminished from 10 to 20 mm. during the height of the action and the pulse became weaker. Increased depth of breathing, sweating and salivation also occurred. The drug's action passed off in a few minutes leaving the heart beating normally.

In the latter half of the investigation a technique was developed

to terminate attacks when the simple injection of the drug was insufficient. If any attack did not stop promptly after the appearance of the flush, the site of the injection was massaged vigorously, with a resulting increase in the intensity of the drug's action. If the attack still persisted the carotid sinuses were compressed alternately, while the drug's action, as judged by the flush, was still undiminished. This was usually immediately successful, although similar carotid compression before the administration of the drug had been ineffective.

Four electrocardiographic records of transitions from paroxysmal tachycardia to normal rhythm after the administration of acetyl-β-methylcholin have been secured. Typical records are shown in Figs. 1 and 2. One shows transient slowing, then a pause followed by immediate resumption of normal rhythm. In the other, cessation of the paroxysm is followed by a period of marked slowing, with prolongation of the $P–R$ interval up to a maximum of 0.32 second, occasional extrasystoles, a few blocked auricular beats and aberrant ventricular complexes suggesting an impairment in bundle-branch conduction. This momentary period of disturbance was followed by normal rhythm, at first at a slow rate. The rate increased as the action of the drug passed off and then slowly diminished. These effects are similar to those which can be produced by vagus stimulation and they should be attributed to this action of the drug. Comparable effects have been observed in the isolated heart in animal experiments.[3]

In a very sick man, C. M. K., a different effect was observed (Fig. 3), the small doses of acetyl-β-methylcholin producing momentary complete block which reverted again to tachycardia. This patient had received 1 gm. of digitalis during the preceding 24 hours and he had been taking smaller amounts previously. As part of the action of digitalis is similar to that of vagus stimulation, and as block so frequently follows an overdose of this drug, it seems reasonable to suppose that the vagus effects of digitalis and acetyl-β-methylcholin might reinforce each other and thus produce block in this instance. But in two experiments on cats,[3] the effect of intravenous injections of acetyl-β-methylcholin on the pulse rate was not changed by the administration of large doses of digitalis.

The results are recorded in Table 1. Those obtained on T. H. in Attacks 9 to 19 were so similar to those secured in the preceding attacks that they have been omitted from this table. A subcutaneous injection of 30 mg. or more of acetyl-β-methylcholin combined with carotid pressure in the few instances noted in the table promptly brought to an end 24 attacks of paroxysmal tachycardia in 7 adult patients. In the case of an emaciated boy (W. S.) smaller doses were successful on 3 occasions. In 2 instances, in T. H., the cessation of the paroxysm was momentary, in the others the period of normal rhythm coincided with that usually occurring

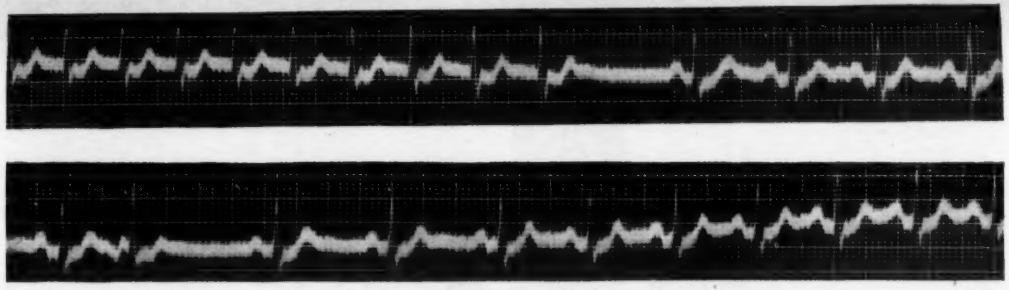

FIG. 1.—Transition from paroxysmal tachycardia to normal rhythm following the administration of acetyl-β-methylcholin.

Lead 2. Thirty milligrams injected 45 seconds before the beginning of the record shown. The lower section is continuous with the upper. (Case A. M. K.)

FIG. 2.—Transition from paroxysmal tachycardia to normal rhythm following the the administration of acetyl-β-methylcholin.

Lead 2. Thirty milligrams injected about 2 minutes before the beginning of the record. The lower section is continuous with the upper. (Case T. H.)

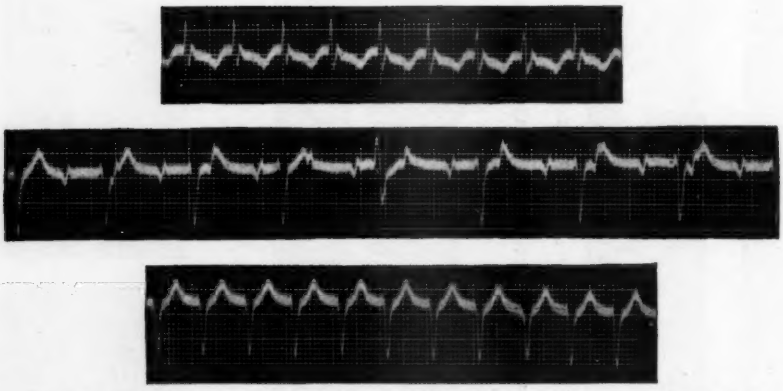

FIG. 3.—Transient heart block following an injection of acetyl-β-methylcholin in a patient with paroxysmal tachycardia who had received large doses of digitalis. Lead 2. The upper record was made before the drug was administered. The middle record was taken about 2 minutes after the injection of 15 mg. The lower record was made about 2 minutes later. (Case C. M. K.)

TABLE 1.—EFFECT OF ACETYL-β-METHYLCHOLIN ON ATTACKS OF PAROXYSMAL TACHYCARDIA.

| Patient. | Age. | Additional diagnoses. | Number of observed attack. | Type of tachycardia by ecg. | Unsuccessful therapy before AβMC. | Dose of AβMC, mg. | Pulse rate before. | Pulse rate after. | Approx. time betw. injec. and cessation of attack (min.). | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|
| F. C. | 26 | Rheumatic heart disease, Class II A | 1 | Auricular | Carotid and ocular pressure; vomiting; 1.2 gm. quinidin | 35 | 180 | 80 | 1¼ | |
| A. M. K. | 49 | Neurocirculatory asthenia | 1 | Auricular | Carotid pressure | 30 | 170 | 120 | ¼ | Patient usually had pulse rate over 100 when not in attack. |
| M. F. | 42 | Three days after thyroidectomy | 1 | Unknown | 10 mg. morphin | 20 | 250 | 200 | .. | Paroxysm continued or resumed. |
| | | | | | | 30 | 250 | 153 | 3 | Paroxysm stopped. Rate similar to that before attack. |
| P. R. | 50 | Polycythemia | 1 | Supraventricular | ..... | 30 | 160 | 114 | 7 | |
| B. M. K. | 21 | Rheumatic heart disease, Class I | 1 | Supraventricular | Carotid pressure | 30 | 176 | 76 | 12 | Carotid pressure during drug's action unsuccessful; attack stopped several minutes later. |
| C. M. K. | 45 | Pelvic abscess; shock; blood pressure not obtainable; fever for 6 months | 1 | Supraventricular | Carotid pressure; 1 gm. digitalis; 0.5 gm. quinidin | 5 | 146 | .. | .. | Momentary heart block, paroxysm resumed. |
| | | | | | | 5 | 150 | .. | .. | One-half hour later—no effect. |
| | | | | | | 10 | 146 | .. | .. | One-half hour later—no effect. |
| | | | | | | 15 | 150 | .. | .. | One-half hour later; transient block resumption of paroxysm with changed ecg |
| W. S. | 19 | Ulcerative colitis; anemia | 1 | .... | Carotid pressure | 20 | .. | .. | 1 | Patient vomited and coughed after attack stopped. |
| | | | 2 | .... | ..... | 10 | .. | .. | ½ | Vomited, defecated after cessation. |
| | | | 3 | Supraventricular | Carotid pressure | 15 | 225 | 85 | ½ | Vomited, defecated after cessation. |
| | | | 4 | .... | ..... | 12 | 204 | .. | .. | Failure. |
| | | | | .... | | 12 | 200 | .. | .. | Second failure 3 hours after first. |
| T. H. | 59 | Arteriosclerosis; cardiac hypertrophy | 1 | Auricular | ..... | 10 | 155 | .. | .. | Failure. |
| | | | | | | 20 | .. | .. | .. | Failure. |
| | | | | | | 30 | 150 | 83 | 4 | Attack stopped but resumed promptly. |
| | | | 2 | Auricular | ..... | 40 | 168 | 60 | 2 | No resumption. |
| | | | 3 | .... | Carotid pressure | 40 | 170 | 70 | 3 | Carotid pressure during drug's action. |
| | | | 4 | .... | Carotid pressure | 50 | 180 | 55 | 4 | Carotid pressure during drug's action. |
| | | | 5 | .... | Carotid pressure | 50 | 160 | 88 | 1½ | |
| | | | 6 | .... | Carotid pressure | 50 | 165 | 70 | 1½ | |
| | | | 7 | | Carotid pressure | 50 | 160 | 75 | 2 | |
| | | | 8 | Auricular | Carotid pressure | 50 | 185 | 70 | 5 | Attack stopped, resumed, stopped and resumed again; after carotid pressure, while drug was still acting, it stopped permanently. |
| W. T. | 60 | Diabetes; arteriosclerosis; gangrene of foot; amputation 15 days ago | 1 | Unknown | Carotid pressure | 30 | 200 | .. | .. | Unsuccessful, very little action of any kind. |
| | | | | | | 50 | 220 | 100 | 2 | Given about 12 minutes after preceding dose. |

between attacks. The few failures occurred with doses under 30 mg. or at the hands of persons who neither massaged the site of the injection nor compressed the carotids during the drug's action. In the case of C. M. K. we started with minute doses because the patient was so very ill, and failed to go higher because we wrongly interpreted the slower rate and increased excursion of the galvanometer string to mean that the attack was over.

In the patients with tachycardia the side effects of the drug usually appeared more slowly and were much less intense than those which followed the administration of similar doses to normal persons. In the arteriosclerotic men T. H. and W. T., doses of 30 mg. or less given during the paroxysm were followed by little demonstrable effect of any kind; 50 mg. produced the usual effects and stopped their attacks. On the other hand doses of 20 mg. or less produced marked side effects on the boy W. S. This difference is doubtless due to slower absorption of the drug from the subcutaneous tissues when the circulation is embarrassed; this must be remembered in choosing the initial dose for any patient. It seems proper to start with small doses. A larger dose may be given as soon as the effects of the preceding have passed off; *i. e.*, in about 15 minutes.

The patients usually had a certain amount of discomfort during the height of the drug's action. It passed off in a few minutes. They all agreed that it was far overbalanced by the relief from distress which followed the cessation of the paroxysm.

The attempt was made to prevent the onset of attacks by giving acetyl-β-methylcholin by mouth. T. H. was having attacks several times a week. He was given the drug 4 times a day and the dosage was increased until he took 4 grams daily. The larger doses appeared to diminish the number of attacks somewhat but they produced an annoying diarrhea. Quinidin was far more effective in preventing attacks and is doubtless a superior drug for this purpose.

*Action on Other Types of Tachycardia.* We have made a few observations on the effect of acetyl-β-methylcholin in tachycardia other than the paroxysmal type. A patient with thyroid disease and a pulse rate of about 150 was given increasing doses of acetyl-β-methylcholin by mouth to a maximum of 600 mg. No slowing of the pulse followed. A subcutaneous injection of 20 mg. increased the pulse rate.

Two patients with constant tachycardia of unknown origin, both young girls, were given by mouth 300 and 40 mg. respectively. After the larger dose the heart rate fell from 110 to 80 and remained at the lower level for 40 minutes. The smaller dose had no effect. The effect of prolonged administration of the drug to such patients has not been ascertained.

*Action in Auricular Fibrillation.* It has been demonstrated that the slowing of the ventricular rate which occurs in this condi-

tion after the administration of digitalis is to be attributed in large part to an action similar to that which follows vagus stimulation. Therefore it seemed possible that acetyl-β-methylcholin, which has a similar action, might likewise cause a desirable slowing of the rate in these cases.

Two cases were selected whose rapid ventricular rate persisted after digitalis had been pushed until nausea and vomiting occurred. The first was given doses of 20 and 40 mg. subcutaneously while connected to the electrocardiograph. The smaller dose did not affect the rate; after the larger the ventricular rate fell from 170 to 112, then returned to 143 after the effects of the drug had passed off. This apparently beneficial effect was accompanied by a good deal of discomfort to the patient from the side effects of the drug. In the second case a subcutaneous dose of 5 mg. caused a fall in rate from 108 to 86. The slowing was momentary and the rate then returned to its original level. Though there was no discomfort in this case the slowing was certainly too transient to be of therapeutic value.

Three cases were selected in which digitalis had failed to produce satisfactory slowing of the ventricular rate. While the digitalis was continued, doses of acetyl-β-methylcholin up to 1 gm. were given by mouth. No slowing could be demonstrated. Therefore we believe that these patients with auricular fibrillation, resistant to digitalis, were not benefited by acetyl-β-methylcholin.

**The Utility of the Vasodilator Action.** *The Effect in Raynaud's Disease.* Four cases of this disease have been studied. They complained that their hands became "bloodless" or blue and painful on exposure to cold in the winter. In each case the hands developed marked cyanosis on immersion in water at 15° C. for 20 minutes. The mildest case, Mrs. G. S., aged 26, suffered only when she drove her automobile in winter. The most severe, Mrs. E. I., aged 60, had gangrenous spots on 2 of her fingers, and the depressed scar of a healed lesion on a third. Essential hypertension complicated this case. Miss F. S. and Mr. M. C., aged 26 and 24, were moderately severe cases but neither had had gangrenous spots. They were otherwise in good health.

Several experiments were made to test the effect of the drug. Skin temperatures were determined by thermal junctions usually fastened to the skin with wide strips of adhesive to prevent evaporation of sweat from cooling the adjacent skin. The skin color was judged by means of the color scale devised for this purpose by Lewis.[5]

F. S., having come in from outside, was placed in a cool room, the temperature being 13° C. At the beginning of the observation the hands ached and were cold and pale. The temperature of the fingers proximal to the nails ranged from 20.1° C. to 22° C. The patient was then given 30 mg. acetyl-β-methylcholin by mouth. One hour later the characteristic action of the drug set in, the blood pressure fell from 102/74 to 90/60, the pulse rate diminished from 92 to 76 and the appearance of the hands com-

pletely changed. They were now warm and redder than normal. The warmest finger was now 32° C., the coldest 24.6°. The discomfort in the hands had lessened but a certain amount still persisted. An hour and a half later the blood pressure had returned to 108/65 and the pulse rate had risen to 88. The hands had become pale again, the skin temperatures had diminished, and now ranged between 22° and 23°. This striking demonstration of the relief of the spasm of Raynaud's disease by means of acetyl-β-methylcholin was repeated on 2 other days, with oral doses of 40 mg. and 100 mg. of the drug.

In 2 other cases, G. S., and E. I., evidence of the vasodilating action of the drug was sought by a comparison of the effects of immersing the hands in cold water at 15° C. for 20 minutes before and during the drug's action. The cyanosis which appeared on the second immersion was not strikingly different from that produced before the drug was given. The changes seen were in the direction of greater redness during the action of the drug. Much more striking was the difference in the patient's sensations. Both stated that on the first immersion the hands became numb and the cold caused no discomfort. But during the drug's action numbness did not occur and they suffered severely from the cold. This may be interpreted as indicating that during the drug's action enough circulation persisted to maintain the function of the nerves. However, the results clearly demonstrate that the drug will not prevent the typical spasm of Raynaud's disease if the hands are exposed to severe cold.

On another occasion spasm was produced in E. I. by immersion of the hands in cold water. After withdrawal the patient lay down and 5 mg. of acetyl-β-methylcholin were administered subcutaneously. Two minutes later the face flushed and a few minute red spots appeared in the cyanosis. Ten minutes later 10 mg. of acetyl-β-methylcholin were administered subcutaneously. This caused marked flushing of the face, and the arms reddened down to the area of cyanosis, but the color of the hands remained unchanged although the skin temperature of the fingers which had been slowly rising, started to climb more rapidly. The action of the drug passed off before any further change could be demonstrated. Obviously the drug had but little effect on such high grades of spasm. This is not surprising as in such conditions the blood flow has practically ceased and the drug would not reach the vessels affected.

In an attempt to relieve the symptoms, acetyl-β-methylcholin was prescribed to the 3 most severe cases.

F. S. was given 20 mg. 3 times a day by mouth. A week later the patient stated that she could detect some slight effect. The dosage was then slowly increased until it reached 100 mg. This dosage was taken 3 times a day and the patient thought her symptoms were improved but relief was not complete. Later the patient took the drug only when she expected to be exposed to cold. This seemed to be a better method, relieving the symptoms while she was in the cold but she continued to have some discomfort when, on reëntering the house, her hands became "hot and swollen."

M. C. was instructed to take 30 mg. 3 times a day. A week later he reported that his symptoms had been almost completely relieved, although the weather had been much colder than in the preceding 2 weeks. He stated that his hands tingled a little when he had exposed them doing outdoor work, but they did not get white, blue and numb as they had done before. The patient was provided with more of the medicine, but he obtained work in another city and the case could not be followed further.

E. I. was first seen in February, 1932. She complained that spasm was present almost every morning while she was doing her housework. She

was, therefore, given two bottles of medicine, each containing acetyl-β-methylcholin and told to take a dose of 100 mg. from the first bottle whenever a spasm occurred. If her hands had not warmed up in an hour, she was to take a similar dose from the second bottle. A week later the patient reported that each time she took the first dose her hands warmed up in 40 or 50 minutes and that they then stayed warm all day. She had taken the second dose only once and was greatly pleased with the relief which she had obtained. Without the patient's knowledge, the contents of the bottle to be taken first were changed to an inert solution with a bitter taste. The bottle containing the medicine to be taken second contained acetyl-β-methylcholin as before. A week later the patient reported that the first medicine was now ineffective and that she had had to take the second medicine every day, and that it had relieved her symptoms in about an hour. This seemed to be sufficient demonstration that the patient was really getting relief from the drug. She was, therefore, told to take 100 mg. every morning which was cold enough to cause symptoms. She was seen a month later and had been taking the medicine regularly. The gangrenous spots on the fingers had healed and she was practically free of symptoms. However, warmer weather had now begun and was certainly a factor in the improvement.

During the following spring and summer she took the drug only on exceptionally cool days, and during the fall she resumed it with increasing frequency until with the coming of winter she again took it daily. In December and January, she took 50 mg. after breakfast "to prevent spasm," whenever the weather was cold. This was not always sufficient. If spasm did set in she took 100 mg. and relaxation always occurred in about an hour. Under this program she insists that she was very much more comfortable than she had been in any winter during recent years. Relief was not complete and during December one of her fingers became sore and an ulcer developed at its tip. This lesion healed in 2 weeks, whereas three similar lesions occurring in former years had not healed until spring.

These observations may be summarized as follows: In Raynaud's disease, the drug does not prevent the development of vascular spasm when the hands are exposed to severe cold. Nor does it cause prompt relaxation of the spasm so produced. However, it can overcome or prevent that which follows more moderate exposure. The patients agreed that their symptoms were in part relieved when the exposure was limited to that encountered in their usual occupations.

*Action in the Occlusive Types of Peripheral Vascular Disease.* In the conditions in which the main vessels of a limb are occluded by organic disease, phenomena suggesting spasm of the unobstructed vessels may often be demonstrated. Therefore, it seemed desirable to ascertain whether these patients might not be benefited by acetyl-β-methylcholin.

The first experiment was made on J. N., aged 28 years, a patient with thromboangiitis obliterans of 2 years' duration. No pulse could be felt in the arteries of either foot and gangrene had necessitated the amputation of the terminal phalanx of both great toes. Three weeks after the operation his feet were exposed to cold air at a temperature of 16° C. The skin temperature of the toes began to fall rapidly and pain soon commenced in both feet. He was then given 300 mg. acetyl-β-methylcholin by mouth. About an hour later the usual signs of the drug's action were observed,

the skin temperature of the toes stopped falling and began to rise and the discomfort disappeared. When the period of observation was terminated 1½ hours later, the temperature of certain toes was still rising, that of other toes was beginning to fall. The maximum increase observed was 1.8° C. As the room temperature did not change the small rise of skin temperature must be attributed to vasodilatation caused by the drug. Similar experiments conducted with doses of 75 and 200 mg. gave essentially similar results.

The same experiment was performed in 2 other cases. In a case of diabetes with threatened gangrene of the left foot a dose of 500 mg. by mouth was followed by a rise of temperature in the more normal foot while that of the threatened foot continued to fall. In another diabetic who had a poor circulation in both feet with severe lesions on one, doses of 100 and 300 mg. did not interrupt the steady fall of skin temperature, though there was other evidence that the drug was acting. These results suggest that the drug will benefit only certain patients, doubtless those in whom vascular spasm is present. But if the vessels are occluded solely by organic disease acetyl-β-methylcholin does not increase the blood supply to the extremity.

When the drug is injected subcutaneously the effect on the peripheral vessels is different. A diabetic whose foot eventually became gangrenous was given a subcutaneous dose of 30 mg. This was followed by a more rapid fall of skin temperature in the foot, evidence that the drug's action diminished the circulation. A similar result was obtained in another case of this disease. Subcutaneous injections appear to be contraindicated in the treatment of such conditions. The fall in blood pressure which follows this method of administration not only diminishes the head of pressure in the peripheral arteries but also may call forth a compensatory vasoconstriction which overcomes the dilator action of the drug.

Since the evidence indicated that the drug, given by mouth, caused an increase in the circulation to the feet of certain cases of occlusive peripheral vascular disease, it has been tried in the treatment of threatened gangrene of the feet. The patients chosen suffered from severe pain in the diseased foot, and an attempt was made to determine the effectiveness of the treatment by the relief secured when the patients did not know whether they were receiving the drug or not.

Mr. C. B., aged 53 years, was known to have had diabetes for 35 years. The toes were cyanotic and vessels of the feet did not pulsate. He had suffered severely from pain in the left foot for 2 weeks and blebs had formed on the toes. The threatened foot was placed in a thermoregulated foot cradle[6] with partial relief but pain persisted at night. Four days later the patient was given 500 mg. of acetyl-β-methylcholin in milk at 6 and 8 P.M. After this the patient had no pain at all; his first comfortable night for almost 3 weeks. The drug was given again the next night and the relief persisted. The night following it was withdrawn and an inert bitter

substance added to the milk which was given as before. This night the patient complained of pain, though it was not as severe as before the drug had been given. The acetyl-β-methylcholin was then resumed for 3 days and discomfort disappeared. Then it was again interrupted and slight pain reappeared, to disappear when the drug was resumed. Therefore, there can be no doubt that the drug relieved the patient's pain. The lesions healed also and recovery was uneventful.

Mr. W. J., aged 58 years, had noted pain in the right foot 3 months ago. One month before admission a small gangrenous patch appeared on the toe and a chronic ulcer on the heel. He went to a hospital and was treated for a month without relief of pain at night. He was then sent to the University Hospital. At that time the left foot was markedly cyanotic and no pulse could be felt below the popliteal space. During his first night in the hospital the patient suffered severe pain. The next day he was given doses of 200 mg. acetyl-β-methylcholin every 2 hours from 4 until 10 P.M. Following this he passed the night without pain and stated that it was the first time this had happened for a month. The next day without the knowledge of the patient an inert mixture was substituted for the acetyl-β-methylcholin. He had no pain that night nor did it recur during his stay in the hospital. Therefore while the initial relief of pain may have been due to the acetyl-β-methylcholin we have certainly failed to prove it.

Mr. E. A., aged 60 years, was known to have had diabetes for 1 year. No pulse could be felt in any artery in his feet. The left foot showed marked rubor, and there was an ulcer between the 4th and 5th toes. Pain had been severe for the last 3 weeks, especially at night. The first night he was given 500 mg. acetyl-β-methylcholin by mouth, the next night 1 gm. No relief followed, and the eventual cessation of pain is certainly not to be attributed to the drug.

Mr. A. C., aged 45 years, had had thromboangiitis obliterans for 3 years. Gangrene had led to amputations below the left knee and above the right ankle. Six weeks ago, after slight trauma, a spot of gangrene developed on the terminal phalanx of the left little finger and the rest of the finger became swollen and cyanotic. Pain in that area soon became intense especially at night. Five doses of morphin sulphate each gr. ¼ (15 mg.) failed to relieve it on one occasion. Two weeks before admission a periarterial sympathectomy had been performed, without relief of pain or other improvement. After admission the pain at night was sufficient to prevent much sleep, he was usually comfortable during the day. He was therefore given 500 mg. of acetyl-β-methylcholin in milk at 6 and 9 P.M. The first night after this treatment pain was much diminished, the second night he had no pain at all. Then the drug was omitted, the milk containing an inert bitter substance being given as before. The night following he had a violent attack, morphin gr. ¼ (15 mg.), phenobarbital gr. ij (120 mg.), amyl nitrite m. iii (0.18 cc.) repeated once, nitroglycerin gr. 1/100 (0.6 mg.) and finally sodium amytal gr. iii (0.18 gm.) were given with but little relief; the pain gradually subsiding 1 hour after the last dose. The next night he had no pain. The night following violent pain returned. After morphin sulphate gr. ¼ (15 mg.) had been ineffective, he was given 500 mg. of acetyl-β-methylcholin by mouth. The pain remained the same for the next 2 hours. Twenty mg. of acetyl-β-methylcholin were then given subcutaneously. The pain in the finger was at once relieved but the side effects of the drug were unusually severe, probably because the action of the previous dose was still in effect. The patient became dyspneic and complained of substernal pain so that atropin sulphate gr. 1/200 (0.3 mg.) was given subcutaneously to stop its action. This did not result in a

return of the pain in the finger, and the patient slept well until morning. The next night there was another violent attack of pain, as severe as the previous night. A smaller dose, 10 mg. of acetyl-β-methylcholin was given subcutaneously. There was no uncomfortable reaction but the pain was not promptly relieved. It subsided gradually.

At this point the administration of 500 mg. of acetyl-β-methylcholin by mouth at 6 and 9 P.M. was resumed. The pain at once diminished and then disappeared completely. The skin temperature of the finger improved and the lesion began to heal. Unfortunately this promising treatment could not be continued as the available supply of the drug was exhausted. Therefore, thoracic sympathectomy was performed. There seems no doubt of the relationship of the drug to the relief of pain in this case.

The effect of acetyl-β-methylcholin on the pain of these 4 cases of occlusive peripheral vascular disease has been illustrated in Fig. 4. In 2 of them the relief may fairly be attributed to the

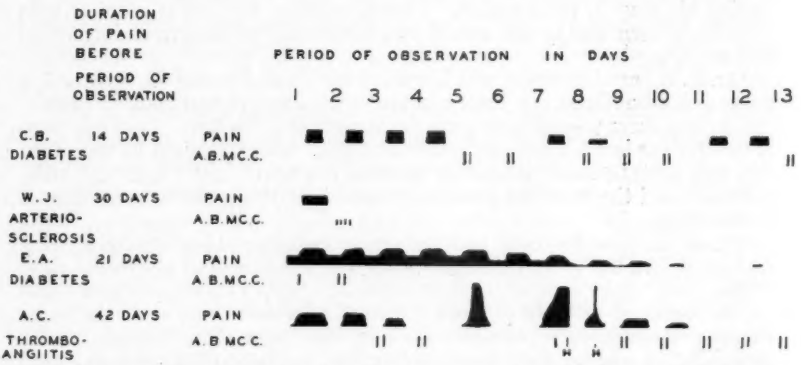


FIG. 4.—Effect of acetyl-β-methylcholin on the pain of 4 cases of obstructive peripheral vascular disease. The larger bars indicate doses of 500 mg., the smaller 200 mg. *H*, indicates a hypodermic injection, the other doses were given by mouth.

drug, in another this may be the case, in the fourth the drug was entirely ineffective. The patients benefited were doubtless those who had some spasm in addition to their organic obstruction.

*Effect on Hypertension and Headache.* Moderate doses of acetyl-β-methylcholin given subcutaneously to patients with hypertension were usually followed by a larger fall of blood pressure than that which occurred in normal persons. The maximum fall observed, from 260/160 to 145/95, occurred after a dose of 25 mg. As the action passed off the pressure returned to its previous height. The patients were all more uncomfortable during the action of the drug than before or after it, and we do not believe that they were benefited.

When the drug was given by mouth many patients exhibited a considerable fall of blood pressure which lasted for ½ hour or longer

without annoying symptoms. Doses of from 50 to 400 mg. have been given on 8 occasions to patients with hypertension who were confined to bed for the day of the test. In 1 patient 200 and 400 mg. failed to cause any effect. In the others the fall of systolic pressure ranged from 38 to 16 mm.

In 3 patients with hypertension relief of headache was reported after taking the drug. One of these was given 100 mg. twice a day by mouth. Her headache returned when the drug was omitted without the patient's knowledge, and it was relieved when the drug was resumed. On the other hand in 3 apparently similar cases the drug did not relieve the headache.

Patient E. I., who has essential hypertension as well as Raynaud's disease, has taken from 50 to 100 mg. of acetyl-β-methylcholin very frequently for 16 months. At the end of this period her blood pressure (220/130) was identical with that found before she began treatment.

*The Effect on Various Intracranial Conditions Possibly Associated With Spasm of Cerebral Vessels.* In a comatose patient, M. B., with hypertension and Cheyne-Stokes breathing, an effect on respiration was demonstrated by Dr. C. F. Schmidt. A subcutaneous dose of 30 mg. was followed by a fall in systolic blood pressure from a maximum of 228 to a minimum of 110 mm., and the breathing became regular and remained so. Twenty-six minutes later 1.2 mg. of atropin sulphate was administered and Cheyne-Stokes breathing reappeared within 5 minutes, the blood pressure rising from 160 to 190 mm. The next day a very similar fall in blood pressure was caused by venesection but the Cheyne-Stokes breathing persisted. Therefore the cessation of Cheyne-Stokes breathing after the drug cannot be attributed to changes arising from the fall in blood pressure, and an action on cerebral vessels is suggested. With this evidence before us we attempted to treat patients having certain ill-defined conditions in which it was suspected that spasm of cerebral vessels might be a factor.

A patient, Mr. J. E., was subject to severe and frequent headaches in one-half of his head. The case was diagnosed cerebral vascular spasm by Dr. W. G. Spiller. The patient was given large doses of the drug, 4 gm. daily for 20 days, and later for 14 days. He was convinced that the pain was materially lessened by the drug. But there was a neurotic element in the case, and suggestion rather than drug action may have caused the improvement.

Another patient, Mrs. A. A., suffered from attacks of vertigo, fairly typical of Ménière's disease. She was not relieved by sedatives or quinin. When given 500 mg. of acetyl-β-methylcholin by mouth she insisted that she was greatly relieved and demonstrated it by walking to the bathroom which she had previously been unable to do without falling. The vertigo returned when the drug was omitted. Its resumption was again followed by improvement.

*Miscellaneous Results.* We tried the effect of a subcutaneous dose of 10 mg. in a case of hemiplegia whose rapid and complete recovery from two previous attacks suggested that it might have been caused by vascular spasm. No beneficial effects were observed.

Encouraged by the relief from headache demonstrated in a few cases of hypertension, we have tried the drug in other types of headache, especially migraine. No relief followed in 2 cases. One patient insisted she was relieved, but in a subsequent attack no relief followed.

Two cases of angina pectoris were given 20 mg. of acetyl-β-methylcholin subcutaneously during an attack. The symptoms of the drug's action appeared as usual but the pain continued unabated. Later nitrites relieved it.

**Discussion of the Clinical Utility of Acetyl-β-methylcholin.** No final evaluation of this active drug can be made on the basis of this, the initial clinical investigation. We have followed only a small number of the leads suggested by its pharmacologic activity. It is of interest to consider other possibilities and point out the limitations of the present investigation.

Acetyl-β-methylcholin may be thought of as a physiologic antagonist to epinephrin, stimulating an opposing system of nerves. This antagonism of action on the heart, bloodvessels, bronchi, and gastro-intestinal tract is obvious. Epinephrin increases the reflexes and produces a sensation akin to excitement in some subjects. In 2 patients with increased reflexes, it could be demonstrated that acetyl-β-methylcholin depressed reflex activity. In the first patient the biceps and triceps jerks were followed by short series of clonic contractions while striking over the brachial plexus resulted in a twitch of the hand. About an hour after the subject had taken 1 gm. of acetyl-β-methylcholin by mouth, while the flush was present, the clonic contractions did not follow the tendon reflexes, and the brachial plexus response could not be elicited. After atropin the original condition promptly returned. In another case the abdominal reflexes could always be elicited by a stroke which traveled between two marked spots in ½ second, timed by a metronome. After a similar dose these reflexes could be elicited only very infrequently by this procedure. When the effect of the drug had passed off the original condition was restored. But in two acute spinal cats prepared by Dr. Grayson McCouch, acetyl-β-methylcholin could not be demonstrated to have any significant effect on the threshold of the flexion reflex.

We have no evidence that the effect of epinephrin on the basal metabolic rate and blood sugar is opposed by acetyl-β-methylcholin.

We have had no opportunity to test the drug's action on the rarer types of cardiac arrhythmia, nor have we made an adequate study

of the effect of its prolonged administration in cases of hypertension; what little evidence we have is not encouraging.

No evidence has been obtained to indicate that the drug is dangerous when administered in the manner and dosage described. It has been given to very sick people. However, its action after subcutaneous injection is so quick and vigorous that we prepare our subjects for what is coming. We tell them that the injection will cause a sudden sensation of warmth in the face, that it may make them breathe hard for a minute, and that this will be followed by sweating and a flow of saliva. The injections are always given with the subject lying down. We have a syringe containing atropin sulphate gr. 1/50 (1.2 mg.) ready at hand. As atropin, given intravenously, would abolish the action of acetyl-β-methylcholin almost immediately, we advise that this precaution be continued. If the drug is given by mouth this is unnecessary. By this route we have given doses up to 4 gm. daily for a prolonged period without the production of uncomfortable or alarming symptoms.

A few untoward effects have been observed. In a patient who had asthmatic attacks infrequently a subcutaneous injection of 20 mg. caused a typical attack. In this case the pulse rate fell from 108 to 60; the flush, instead of being confined to the face and neck, was generalized; the blood pressure, instead of falling, rose from 138/90 to 170/98. Atropin sulphate gr. 1/75 (0.9 mg.) was given subcutaneously and relief began within 2 minutes. Much milder asthmatic attacks have followed the taking of large doses by mouth in patients subject to asthma, and the same occurred in one elderly subject not known to have had asthma. Therefore, it seems proper to recommend caution in giving subcutaneous injections or large doses by mouth to patients who suffer from asthma and other conditions relieved by adrenalin, a physiologic antagonist of the cholins.

Both dyspnea and substernal pain followed the injection of 20 mg. into a patient who had received 1 gm. by mouth a short time before. This was also cut short by atropin.

In 2 patients who had been vomiting the subcutaneous injection of 10, 20 and 40 mg. was followed by vomiting. No other patients have vomited or indeed felt nauseated after subcutaneous administration. The slight epigastric discomfort which some persons complained of after taking the drug by mouth was almost always prevented by administering it in milk.

One subject complained of a disturbance of accommodation after taking 300 mg. by mouth. This passed off within 30 minutes. Some effect on accommodation is to be expected from the pharmacologic properties of the drug, but no other subjects noticed it.

In 1 case of paroxysmal tachycardia in a very sick patient, the subcutaneous administration of the drug caused momentary com-

plete heart block. The large amount of digitalis which this patient had received may well have been a factor in this case. However, a few blocked beats have been demonstrated in other patients during the transition from paroxysmal tachycardia to normal rhythm. Extrasystoles also occurred during this transition. In 1 case coupled beats were found after the administration of large doses by mouth.

Therefore, it is evident that this drug, like all other active drugs, may produce untoward effects against which the physician must be on his guard. But only 3 times in our experience have these effects been severe enough to necessitate their termination by atropin.

The most spectacular action of the drug is the immediate termination of the attacks of paroxysmal tachycardia, of the auricular or supraventricular type. We know of no other drug which will produce this effect. We have evolved a technique for this purpose.

If our experience is typical the great majority of these attacks can be stopped by the drug alone. If this is insufficient, carotid pressure during the drug's action is usually successful. In the prevention of such attacks acetyl-β-methylcholin proved inferior to quinidin in 1 case. We have had no opportunity of testing the effect of the drug on the ventricular type of paroxysmal tachycardia.

In other types of tachycardia, acetyl-β-methylcholin will at times cause slowing. Whether it can be used with benefit to these patients is as yet undecided.

The increased gastro-intestinal tone and peristalsis which followed the exhibition of acetyl-β-methylcholin have caused striking relief in certain cases of abdominal distention.[7] But the effect on other types of gastro-intestinal dysfunction has not yet been investigated.

Acetyl cholin has been advocated for the treatment of the spastic types of peripheral vascular disease,[8] and relief of pain following its use in senile arteritis has been reported.[9] Acetyl-β-methylcholin has a similar vasodilating action, it is much more stable than acetyl cholin and it produces more prolonged effects. It lacks certain undesired side effects produced by the latter drug. Its peripheral vasodilating action in Raynaud's disease and in certain cases of obstructive arterial disease can be easily demonstrated. The patients in which it has been used have been symptomatically relieved and when an attempt was made to substitute an inert solution for one containing the drug they detected it at once. Acetyl-β-methylcholin seems superior to acetyl cholin in every particular for the treatment of these conditions.

**Summary.** Acetyl-β-methylcholin has been employed in the treatment of certain types of cardiovascular disease. This drug causes effects similar to those following stimulation of the vagus and other parasympathetic nerves. It also causes peripheral vaso-

dilatation. After subcutaneous injection it has a prompt and vigorous action. Given by mouth the effects are much milder.

The untoward effects of the drug are described. They can be immediately abolished by atropin.

Injected subcutaneously, the drug has caused the immediate termination of 24 attacks of paroxysmal tachycardia in 9 patients. In 7 the attacks were of the auricular or supraventricular type, in the other 2 no electrocardiograms were secured. In most of the attacks carotid pressure and other means had been tried unsuccessfully before the drug was given. In a few instances a combination of the drug's action and carotid pressure terminated attacks which could not be stopped by carotid pressure alone. Failure was very infrequent except when the dosage was inadequate. Electrocardiograms showed the transition from the paroxysm to normal rhythm.

The vascular spasm of Raynaud's disease, when excited by mild degrees of cold, was relieved or prevented by the action of the drug administered by mouth. The spasm following exposure to severe cold was but little affected. The discomfort of 3 such patients was in part ameliorated by taking the drug by mouth during cold weather.

The drug repeatedly caused a rise of the skin temperature of the feet in a case of thromboangiitis obliterans. It relieved the pain in certain cases of threatened gangrene from obstructive peripheral vascular disease. But no evidence of a peripheral vasodilator action could be secured in certain other cases of this type.

The drug caused a temporary reduction of blood pressure in most cases of hypertension. In some such cases relief from headache followed the exhibition of the drug. In other apparently similar cases no relief was secured.

In 1 case Cheyne-Stokes respiration was abolished by the drug. Two other patients, in whom spasm of cerebral vessels may have been a factor, reported improvement of headache and vertigo after taking the drug.

The possible utility of acetyl-β-methylcholin in certain other disease conditions is discussed.

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# A DIAGNOSTIC TEST FOR INFECTIOUS MONONUCLEOSIS.

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In a recent article[1] the presence of a rather high concentration of heterophil antibodies, demonstrable in the form of sheep cell agglutinins, has been described in the active stages of 4 cases of infectious mononucleosis. Since then tests for heterophil antibodies have been made in over 2000 cases representing various clinical entities, including additional cases of infectious mononucleosis. The diagnostic value of the test has become increasingly evident. In the present report the results of these tests, with a few modifications of the method, are recorded. No attempt is made to review in detail the development of knowledge of heterophil antigens and antibodies, but a few statements relative to the nature of the phenomenon involved seem desirable.

Forssman[2] observed that emulsions of the tissues (other than blood cells) of the guinea-pig, cat and horse stimulate the production of lysins for sheep red blood corpuscles, just as sheep erythrocytes themselves do when injected into rabbits. Subsequently, the term Forssman antigen or heterophil antigen has been applied to materials which have this property. Apparently the substances which contain the heterophil antigen are widespread throughout the animal kingdom and to a lesser degree among bacteria as evidenced by the ever increasing list of carriers of heterophil antigen.

Comparatively few bacterial species, however, have been investigated as to their content of heterophil antigens. Such antigens have been found in strains of B. paratyphosus B, B. enteritidis (Gaertner),[3] B. dysenteriæ (Shiga),[4] a particular strain of B. lepisepticus[5] and recently in various types of pneumococci.[6] The nature of these bacterial heterophil antigens is not thoroughly known. Some appear to be identical with those present in sheep cells or guinea-pig kidney, but others differ somewhat. That the heterophil antibodies are distinct from specific bacterial agglutinins and precipitins is well demonstrated by absorption tests. The possible part played by these heterophil antigens in the development of immunity to various diseases has yet to be demonstrated.

Only recently has the Forssman phenomenon found clinical application. Through the work of Davidsohn,[7,8] Deicher,[9] Perry and Rhodes,[10] Paul and Bunnell,[1] and others, the presence of hemolysins and agglutinins for sheep cells in low dilutions of supposedly normal human sera have been repeatedly demonstrated. Friedberger and his co-workers[11] have shown that there is a definite age distribution

of this heterophil antibody content, which rises from zero at birth to reach a peak at about the 12th year and then falls gradually through subsequent decades. Paul and Bunnell[1] confirmed this finding in a study of 275 hospitalized patients. There is some disagreement among different investigators as to the percentage of individuals who show heterophil agglutinins in a serum dilution of 1 to 4, but there is apparent complete agreement that the titer rarely exceeds 1 to 8 in normal human serum. Following the injection of horse serum, which is a known carrier of heterophil antigen, an increased titer of heterophil antibodies in the blood of patients suffering from horse serum disease was first reported by Davidsohn[7,8] in 1929. Agglutination titers ranging from 1 to 32 to 1 to 64 were found at the height of this disease or shortly afterward. He concluded from this that an agglutinin titer for sheep cells of 1 to 32 or higher is suggestive of horse serum sickness in the more or less recent past. Ramsdell and Davidsohn[12] in 1930 reported 26 cases, representing various clinical conditions severe enough to occasion hospital residence, on which determinations of sheep cell agglutinins in the serum were made. In none of the cases, except 1 case of severe diabetes mellitus, which was receiving intensive insulin treatment, was an agglutinin titer greater than 1 to 8 found. Paul and Bunnell[1] in 1932, reported a low titer of sheep cell agglutinins in 323 hospitalized patients representing a variety of clinical conditions. With one exception (a fatal case that was classified as possibly aplastic anemia, but may well have been a case of infectious mononucleosis with complicating acute hemorrhagic nephritis similar to those reported by Tidy and Daniel[13]) no appreciable increase in the sheep cell agglutinin titer was found except in cases of serum disease and infectious mononucleosis.

METHODS. The method we have employed in determining the concentration of the heterophil agglutinins for sheep cells in human sera was reported previously.[1] The serum, from 5 to 8 cc. of human blood obtained as for a Wassermann test, is utilized for the procedure. For sake of conformity in results it is important to use a standard type of agglutination tube. We have found a tube 100 mm. in length and 10 mm. in diameter most satisfactory and have used it in all our tests, as a slight effect upon the readings is noticed with varying sized tubes. The use of a 2 per cent suspension of sheep cells is likewise desirable, as a heavier suspension interferes with the agglutination phenomenon.

If the serum is inactivated properly and the procedure carried out as described, there should be no hemolysis in the tubes to confuse the readings. (In serum which contains bile the sheep cells are usually hemolyzed and the tests unsatisfactory.)

RESULTS. The results of the investigation of various clinical conditions here reported are presented in Table 1. It will be seen that the marked increase in heterophil agglutinins for sheep cells previously reported in infectious mononucleosis has not been encountered in other conditions. In determinations that we have made

on over 2000 individuals, the presence of a consistently low titer is outstanding. In Table 1 the range of agglutinin titers of 437 hospitalized cases representing 76 clinical conditions, including 22 cases of serum disease but excluding the 15 cases of infectious mononucleosis, is shown. In addition Table 2 includes the range of titers found on testing 1600 sera obtained from the Wassermann laboratory. These are arranged in groups according to titer, as diagnoses and ages were not available.

TABLE 1.—SHEEP CELL AGGLUTININS IN MISCELLANEOUS CONDITIONS.

| Clinical conditions in groups. | No. of cases. | Range of titer. | Dilutions of patient's serum. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 1/2 | 1/4 | 1/8 | 1/16 | 1/32 | 1/64 | 1/128 |
| Normals | 36 | Max. | ++ | + | + | ± | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Psychosis, toxemia preg., normal preg., metal poisoning | 28 | Max. | + | + | ± | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Fractures, burns, myositis | 18 | Max. | + | + | ± | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Obesity, gen. arteriosclerosis, diabetes, malnutrition, acute and chronic nephritis, rickets | 27 | Max. | + | + | + | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Peptic ulcer, gall bladder disease, pelvic inflammatory disease, ovarian cysts, malignancy, catarrhal jaundice | 32 | Max. | + | + | ± | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Common cold, grippe, influenza, follicular tonsillitis, otitis media, acute cervical adenitis, acute bronchitis, bronchopneumonia, lobar pneumonia, empyema | 48 | Max. | ++ | ++ | + | ± | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Bronchial asthma, pulmonary tuberculosis, erythema nodosum | 33 | Max. | ++ | ++ | + | ± | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Acute rheumatic fever, rheumatic arthritis, rheumatic heart disease | 35 | Max. | ++ | + | + | ± | ± | − | − |
| | | Min. | ± | − | − | − | − | − | − |
| Syphilis: Primary, secondary, tertiary and congenital | 16 | Max. | + | + | ± | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Erysipelas, scarlet fever, misc. strep. infections, diphtheria, typhoid, measles, chickenpox, pertussis, mumps, meningococcus meningitis, Vincent's angina | 89 | Max. | ++ | + | + | ± | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Primary, secondary and aplastic anemia, erythroblastic anemia, purpura hemorrhagica, Banti's disease | 26 | Max. | +++ | +++ | ++ | ± | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Hodgkin's disease, agranulocytosis, acute and chronic—myelogenous and lymphatic leukemia, malignant thymoma, benign lymphadenosis | 27 | Max. | + | + | + | − | − | − | − |
| | | Min. | − | − | − | − | − | − | − |
| Serum disease | 22 | Max. | +++ | +++ | +++ | +++ | +++ | ++ | − |
| | | Min. | +++ | ++ | ± | − | − | − | − |

In none of the clinical conditions simulating infectious mononucleosis or those with which it might be confused have we been able to demonstrate any appreciable increase in the agglutinin titer. Cases of acute rheumatic fever and rheumatoid arthritis may occasionally show a plus minus agglutination in a titer of 1 to 32 but none higher has been encountered. Vincent's angina and agranulo-

cytic angina show no abnormal increase of heterophil agglutinin titer. Several of the blood dyscrasias, including acute and chronic myelogenous and lymphatic leukemia, likewise show no increase of agglutinins above the normal level. While clinical conditions associated with bacterial etiologic agents show a tendency to a slightly higher titer than is the case in non-bacterial diseases, the increase is small. Furthermore, the degree of agglutination as well as the titer is strikingly less than in infectious mononucleosis. In serum disease following the injection of horse serum, however, there is a distinct rise in the agglutinin titer though not as high as is usually found in infectious mononucleosis. Likewise, the type of agglutination in the cases of serum disease resembles more closely the reaction found in the cases of infectious mononucleosis.

TABLE 2.—SHEEP CELL AGGLUTININS ON 1600 INDIVIDUAL SERA OBTAINED FROM WASSERMANN LABORATORY ON WHICH DIAGNOSES AND AGES WERE NOT AVAILABLE.

| Sera. | | No. cases showing various readings in the same titer. | Range of agglutinin titers and readings on individual sera. | | | | |
|---|---|---|---|---|---|---|---|
| Number. | Per cent. | | 1/4. | 1/2. | 1. | 1/16. | 1/32. |
| 651 | 40.7 | 651 | − | | | | |
| 373 | 23.3 | 264 | ± | | | | |
| | | 104 | + | | | | |
| | | 5 | ++ | | | | |
| 355 | 22.2 | 50 | ± | ± | | | |
| | | 210 | + | ± | | | |
| | | 76 | + | + | | | |
| | | 19 | ++ | + | | | |
| 144 | 9.0 | 19 | + | ± | ± | | |
| | | 53 | + | + | ± | | |
| | | 6 | + | + | + | | |
| | | 30 | ++ | + | ± | | |
| | | 22 | ++ | + | + | | |
| | | 14 | ++ | ++ | + | | |
| 64 | 4.0 | 5 | + | + | ± | ± | |
| | | 24 | + | + | + | ± | |
| | | 5 | + | + | + | + | |
| | | 3 | ++ | + | ± | ± | |
| | | 8 | ++ | + | + | ± | |
| | | 13 | ++ | ++ | + | ± | |
| | | 3 | ++ | ++ | + | + | |
| 13 | 0.8 | 3 | ++ | ++ | ++ | ± | |
| | | 5 | + | + | + | ± | ± |
| | | 8 | ++ | + | + | ± | ± |

In sharp contrast to the findings listed in Tables 1 and 2 are the observations on 15 cases of infectious mononucleosis presented in Table 3. These cases can be classified, on the basis of duration of symptoms, into two groups, the acute cases usually more severe and generally presenting a more pronounced increase in the agglutinin titer for sheep cells, and the subacute cases which run a more prolonged course and show an agglutinin titer not greater than 1 to 128 and usually only 1 to 64. The duration of the acute case is usually 14 to 21 days, while the course of the subacute cases is prolonged for a month or more. Though there is considerable variation in the

TABLE 3.—SHEEP CELL AGGLUTININS IN INFECTIOUS MONONUCLEOSIS.

| No. | Type of case. | Age. | Stage of disease serum was obtained. | Duration of illness. | Dilutions of patient's serum. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1/2. | 1/4. | 1/8. | 1/16. | 1/32. | 1/64. | 1/128. | 1/256. | 1/512. | 1/1024. | 1/2048. | 1/4096. | 1/8192. |
| 1 | Acute | 22 | 7th day<br>13th day<br>11 months later | 13 days | +++<br>+++<br>++ | +++<br>+++<br>+ | +++<br>+++<br>+ | +++<br>+++<br>− | +++<br>++<br>− | +++<br>++<br>− | +++<br>+<br>− | ++<br>−<br>− | ++<br>−<br>− | +<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| 2 | Acute | 21 | 10th day<br>19th day<br>4 months later | 21 days | +++<br>+++<br>++ | +++<br>+++<br>+ | +++<br>+++<br>− | +++<br>+++<br>− | +++<br>+++<br>− | +++<br>+++<br>− | +++<br>++<br>− | ++<br>+<br>− | +<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| 3 | Acute | 25 | 9th day | 16 days | +++ | +++ | +++ | +++ | +++ | ++ | ++ | + | + | + | + | ± | − |
| 4 | Subacute | 16 | 6 months before<br>10th day<br>16th day<br>26th day<br>1 month later | 30 days | ±<br>+++<br>+++<br>++<br>− | −<br>++<br>++<br>++<br>− | −<br>++<br>++<br>++<br>− | −<br>+<br>+<br>+<br>− | −<br>±<br>+<br>+<br>− | −<br>−<br>+<br>±<br>− | −<br>−<br>±<br>−<br>− | −<br>−<br>−<br>−<br>− | −<br>−<br>−<br>−<br>− | −<br>−<br>−<br>−<br>− | −<br>−<br>−<br>−<br>− | −<br>−<br>−<br>−<br>− | −<br>−<br>−<br>−<br>− |
| 5 | Subacute | 24 | At onset<br>14th day<br>21st day<br>28th day | 31 days | +<br>++<br>++<br>+ | +<br>++<br>+<br>+ | −<br>++<br>+<br>+ | −<br>+<br>+<br>± | −<br>+<br>+<br>± | −<br>±<br>±<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− | −<br>−<br>−<br>− |
| 6 | Subacute | 25 | 15th day | 30 days? | ++ | ++ | ++ | ++ | + | ± | − | − | − | − | − | − | − |
| 7 | Acute | 15 | 7th day<br>10th day<br>18th day | 21 days | +++<br>+++<br>++ | +++<br>+++<br>++ | +++<br>+++<br>+ | ++<br>+++<br>+ | +<br>++<br>+ | +<br>++<br>± | ±<br>+<br>− | −<br>+<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| 8 | Acute | 45 | 7th day | ? | ++ | ++ | ++ | + | + | + | ± | − | − | − | − | − | − |
| 9 | Acute | 19 | 6th day<br>14th day | 14 days | ++<br>++ | ++<br>+ | ++<br>+ | +<br>+ | +<br>± | ±<br>± | ±<br>− | −<br>− | −<br>− | −<br>− | −<br>− | −<br>− | −<br>− |
| 10 | Acute | 23 | 5th day<br>16th day<br>22d day | 22 days | +++<br>++<br>++ | +++<br>++<br>++ | ++<br>++<br>++ | ++<br>++<br>+ | ++<br>+<br>± | +<br>−<br>− | ±<br>−<br>− | ±<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| 11 | Acute | 20 | 4th day<br>4 weeks after onset | 18 days | +++<br>+ | +++<br>± | +++<br>− | ++<br>− | +<br>− | ±<br>− | −<br>− | −<br>− | −<br>− | −<br>− | −<br>− | −<br>− | −<br>− |
| 12 | Acute | 26 | 14th day | 20 days | +++ | ++ | ++ | ++ | ++ | + | + | − | − | − | − | − | − |
| 13 | Acute | 20 | 10th day | ? | +++ | +++ | +++ | +++ | ++ | ++ | + | − | − | − | − | − | − |
| 14 | Acute | 20 | 4th day | 16 days | +++ | +++ | +++ | +++ | ++ | ++ | + | − | − | − | − | − | − |
| 15 | Acute | 21 | 21st day | 22 days | +++ | +++ | ++ | + | + | ± | − | − | − | − | − | − | − |

agglutinin titer in the group of acute cases, they tend to show a higher titer than the subacute cases. The height of the agglutinin response is fairly well correlated with the severity of the illness and distinctly related to the stage of the disease in which the serum for the test is obtained. This relationship and also the relationship of the associated pathologic lymphocytosis can be better understood by a study of the following case report and graphic presentation of the course of the disease.

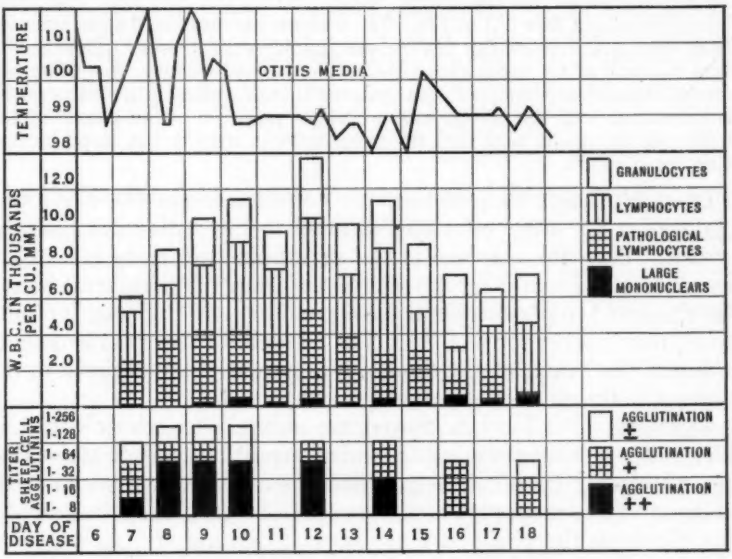


FIG. 1.—Case 7. Infectious mononucleosis.

**Case Report.** J. W. (Case 7, Table 3), a white American schoolboy, aged 15 years, was admitted to the New Haven Hospital on the evening of December 9, 1931, complaining of fever and dull pain in the right lower quadrant.

He gave a previous history of lassitude, drowsiness, anorexia, slight pain about the umbilicus and fever of about 5 days' duration. Twelve hours after administration of a dose of citrate of magnesia he began to complain of a severe dull pain in the lower abdomen which later localized in right lower quadrant and brought about his hospitalization for acute appendicitis.

On admission the patient's temperature was 101° F. The throat was slightly injected and small ulcerative areas were present on the surface of the enlarged lingual tonsil. The tonsillar fossæ were clear. There was a moderate painless enlargement of the cervical, axillary and inguinal lymph nodes, which were discrete and moderately firm. The liver and spleen were not palpable. There was slight tenderness on deep pressure in both lower quadrants without muscle spasm. The total leukocyte count on December 10, 1931, was 5500, with 58 per cent lymphoid cells and 1 per cent mononuclears. The throat culture showed an essentially normal mouth flora. A stained smear from the ulcerative areas on the lingual tonsil showed numer-

ous diphtheroids and a moderate number of fusiform bacilli with a rare spirillum. Kahn and Widal tests were negative. From a culture of the blood in Savita broth a few diphtheroid-like organisms were isolated after 7 days' incubation. A stool culture was negative for pathogenic organisms.

On December 11, 1932, the patient had a spontaneous epistaxis, the adenopathy had become more pronounced and the spleen was easily palpable, 2 cm. below the costal margin. The leukocyte count at this time was 6100, with 85 per cent lymphoid cells and 3 per cent large mononuclears. Forty-two per cent of the lymphoid cells were typical pathologic lymphocytes which have been so well described by Downey and McKinley,[14] the cells in this case corresponding closely to their so-called Type I. Sheep cell agglutinins at this stage were determined for the first time and found to be present in a titer of 1 to 128. The temperature remained at an elevated level with irregular swings for 5 days following admission. During this time bilateral otitis media developed. The patient's course was otherwise uneventful and at time of discharge a notable decrease in the adenopathy had occurred and the spleen was no longer palpable. The course of the sheep cell agglutinin titer and the progressive change in the blood picture is shown in Fig. 1.

It is of interest to note that the development of the heterophil agglutinins for sheep cells runs parallel to the pathologic lymphocytosis. With the decrease in the agglutinin titer there is a disappearance of the pathologic lymphocytes from the peripheral blood. An absolute lymphocytosis, however, composed of normal lymphocytes, may persist for months. The increase in the total leukocyte count at the height of the disease is apparently due entirely to the increase in the number of pathologic lymphocytes.

**Summary.** We have employed the sheep cell agglutinin test in over 2000 cases representing 76 clinical conditions. With the exception previously noted, namely, serum disease, we have been unable to demonstrate an appreciable increase of heterophil agglutinins for sheep cells in the sera above the normal dilution of 1 to 8. In 15 cases of infectious mononucleosis we have found a consistent increase in all cases. The titers, ranging from 1 to 64 to 1 to 4096, apparently depended to a considerable extent upon the stage of the disease at which the serum was obtained and upon the severity of the illness. None of the common conditions manifesting a similar clinical picture such as acute adenitis, tuberculous or syphilitic adenitis, Hodgkin's disease, acute or chronic lymphatic or myelogenous leukemia, aplastic anemia, purpura hemorrhagica, agranulocytic angina or Vincent's angina, has shown an increase in heterophil agglutinin titer.

**Conclusions.** In view of these findings it seems justifiable to accept the test for heterophil agglutinins for sheep cells as a valuable diagnostic procedure in differentiating infectious mononucleosis from a number of clinical conditions of a far more serious nature.

Cases presenting a suggestive clinical and blood picture whose blood serum shows an agglutination for sheep cells in a dilution of at least 1 to 64 can apparently safely be diagnosed as infectious mononucleosis, and a favorable prognosis given.

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## AN INSTANCE OF LYMPHATIC LEUKEMIA FOLLOWING BENZOL POISONING.

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This rather remarkable circumstance of a patient under treatment and observation for chronic benzol poisoning, gradually developing the picture of a full-blown leukemia, is of sufficient interest to merit its report in essential detail.

**Case Report.** A white male, aged 58 years, employed by a can company, was first seen May 21, 1924, complaining of weakness, dizziness, dyspnea and "a puffing noise in the head." History disclosed that his work was to "truck" can ends from the foot of a conveyor to the warehouse. The can ends, rimmed with a solution of rubber in benzol, were delivered to him by a conveyor, the benzol evaporating from the rubber mixture "en route."

He first noted weakness and dizziness April 4. On May 1, weakness in the lower extremities forced him to stop work and consult his family physician who found his "blood thin," administering "iron" injections and "pills" by mouth. There was no past history of infections except for two attacks of "chills and fever" lasting 2 weeks, disappearing without special medication, 8 years and 5 years before the present illness. There was no history of anemia or previous weakness.

*Physical examination* showed a short, obese, pale man with a sallow tint to skin. Several teeth missing. Moderate degree of peridentosis present. Palpable posterior cervical and inguinal nodes. Blood pressure: systolic, 130; diastolic, 80. Heart slightly enlarged to the left by percussion. The first heart sound was feeble over lower precordium, accompanied by a soft, blowing systolic murmur heard best over the pulmonic area. Chest showed impaired resonance at the right base, with harsh breath sounds but no râles at this area. Abdomen protuberant, rounded. The edge of the liver was palpable 3 cm. below the costal border, slightly tender. Spleen not felt. Over skin of trunk, extensor surface of arms, and over both lower extremities

below the knees were small, dull, red to purplish-red spots from 0.5 mm. to 1 mm. in diameter. They do not fade on pressure and represent typical purpuric areas. The "tourniquet test" is positive. The knee jerks are sluggish. No sensory disturbances made out.

The *blood studies* at this time showed hemoglobin 50 per cent (Newcomer); red cells, 1,530,000; white cells, 8100 per c.mm. Differential: neutrophils, 62; lymphocytes, 32; monocytes, 6 per cent. Platelet count, 68,000 (Reese and Ecker[1]). The red cells showed anisocytosis, a few large red cells, some showing polychromatophilia.

The author had seen 4 cases of typical benzol poisoning from the same plant during the previous year. Therefore, with the history of exposure and the blood findings detailed above, with the spleen not palpable and no immature white cells appearing on any of the smears, a diagnosis of benzol poisoning was made.

*Clinical Course.* On June 4, 2 weeks after the first visit, hemorrhage from the nose began. His red and white cell counts began to decrease. Platelets were 74,000. He was admitted to a hospital and received a transfusion of 700 cc. whole blood. Within 3 days the nasal bleeding ceased and after 1 week he was able to leave the hospital.

On July 7, he began reporting to the author for observation and treatment. Three times per week intravenous injections of sodium cacodylate were administered, 1 cc. of a 19 per cent solution. In addition he took Blaud's powder, 0.3 gm. after each meal. On September 9, nasal bleeding again occurred; also a pigmented papular mole 0.5 cm. in diameter on the back of his chest continually oozed blood. He was readmitted to the hospital and transfused with 600 cc. whole blood. After 1 week, bleeding having ceased, he was discharged from the hospital. Improvement progressed slowly in red cell count and hemoglobin, but the platelets remained low in number. The accompanying chart of his blood-counts, in chronological order, show his progress. By the end of March, 1925, he was allowed to take up light work about the exterior of the plant. In June, the notes state, "Doing light work and progressing favorably." The platelets lagged behind the other formed elements of the blood. The red cells showed central pallor and anisocytosis. By January, 1926, the platelets had reached 116,000; the red cells and hemoglobin seemed to have reached a new level of blood production, considerably lower than the normal standard but sufficient to maintain him at a comfortable working status. His work called for very little actual physical exertion.

On March 19, 1926, it was noted that his white count had risen to 13,200, with polymorphonuclear neutrophils, 36; eosinophils, 1; lymphocytes, 56; monocytes, 6; neutrophilic myelocytes, 1 per cent. The table shows the blood counts as the leukemia progressed and accompanying charts illustrate in graphic form the blood picture from early symptoms of the benzol poisoning to his demise from leukemia.

He remained at light work throughout 1926, the white cells gradually rising and hemoglobin and red cells gradually falling. By January 22, 1927, the white cell count had risen to 49,500, with polymorphonuclear neutrophils, 9; eosinophils, 1; lymphocytes, 89; monocytes, 1 per cent. Many of the lymphocytes now were somewhat larger than the normal lymphocyte with a paler staining, less dense nucleus than one sees in a normal smear. They were not definitely lymphoblasts, so are included under the designation lymphocytes. McJunkin's oxydase stain on January 22, 1927, showed granular cells 16, non-granular 84 per cent. Patient stated he felt well except for slight weakness and dyspnea and he did not wish to give up his work. On July 8, on account of weakness and dyspnea he was forced to stop work. On December 16, the white cell count was 108,300 with neutrophils, 4; lymphocytes, 92; lymphoblasts, 3; neutrophilic myelocytes, 1 per cent.

The hemoglobin was 39 per cent, and red blood cells 1,520,000. Daily doses of 6 vials Lilly's Liver Extract No. 343 were tried. The reticulocyte rise was not above 1 per cent. On February 1, 1928, he was readmitted to the hospital and on February 16, death occurred. The clinical diagnosis was lymphatic leukemia.

TABLE 1.—WHITE BLOOD CELL AND PLATELET COUNTS EXTENDING OVER 3 YEARS, 8½ MONTHS.

| Date. | Total white count per c.mm. | Neutrophils, per cent. | Basophils, per cent. | Eosinophils, per cent. | Lympho. per cent. | Mono. per cent. | Platelets in thousands per c.mm. |
|---|---|---|---|---|---|---|---|
| 5/21/24 | 8,100 | 62 | .. | .. | 32 | 6 | |
| 6/ 4/24 | 4,600 | 50 | .. | 3 | 41 | 6 | 74 |
| 7/ 7/24 | 3,400 | 32 | .. | 1 | 59 | 8 | 64 |
| 8/25/24 | 4,400 | 70 | 1 | .. | 22 | 7 | 72 |
| 9/30/24 | 7,120 | 50 | .. | 1 | 40 | 9 | 68 |
| 11/11/24 | 5,300 | 68 | .. | 1 | 25 | 6 | 74 |
| 12/10/24 | 8,200 | 61 | .. | .. | 32 | 7 | 68 |
| 2/ 6/25 | 7,400 | 59 | .. | 1 | 37 | 3 | 70 |
| 3/17/25 | 5,000 | 45 | .. | .. | 53 | 2 | 72 |
| 5/18/25 | 8,320 | 64 | 1 | 1 | 31 | 3 | 88 |
| 8/24/25 | 9,300 | 58 | .. | .. | 37 | 5 | 114 |
| 1/12/26 | 7,800 | 58 | .. | .. | 38 | 4 | 116 |
| 3/19/26 | 13,200 | 36 (1) | .. | 1 | 56 | 6 | 74 |
| 3/30/26 | 12,400 | 34 | .. | .. | 57 | 9 | |
| 4/16/26 | 14,000 | 46 | 1 | 1 | 43 | 9 | 68 |
| 6/22/26 | 16,920 | 52 | .. | .. | 43 | 5 | 88 |
| 1/10/27 | 49,500 | 9 | .. | 1 | 89 | 1 | 160 |
| 3/21/27 | 42,400 | 28 | .. | .. | 71 | 1 | 120 |
| 4/18/27 | 56,000 | 17 | .. | .. | 81 | 2 | 100 |
| 5/ 9/27 | 58,000 | 16 | .. | .. | 82 | 2 | 112 |
| 5/25/27 | 55,000 | 16 | .. | .. | 83 | 1 | 76 |
| 6/ 9/27 | 64,400 | 12 | .. | .. | 87 | 1 | 132 |
| 7/ 8/27 | 63,000 | 8 | .. | .. | 92 | .. | 66 |
| 7/21/27 | 44,400 | 6 | .. | .. | 90 | 4 | |
| 7/30/27 | 70,600 | 12 | .. | .. | 88 | .. | 86 |
| 9/22/27 | 79,400 | 5 | .. | .. | 92 | 3 | 54 |
| 10/31/27 | 69,500 | 9 | .. | .. | 89 | 2 | 40 |
| 12/ 8/27 | 71,600 | 3 | 1 | .. | 93 | 3 | 34 |
| 12/16/27 | 108,300 | 4 (1) | .. | .. | 92 (3) | | |
| 1/ 4/28 | 89,000 | 2 | .. | .. | 95 | 3 | 30 |
| 1/20/28 | 94,000 | 3 (1) | .. | .. | 94 | 2 | 50 |
| 2/ 1/28 | 108,000 | 4 | .. | .. | 96 | .. | 60 |
| 2/13/28 | 140,000 | 2 | .. | .. | 98 | .. | 34 |

( ) = Immature cells.

*Postmortem Examination.* (By Drs. G. Y. Rusk and S. R. Mettier, 6 hours after death). The body was well developed and moderately obese. The skin and mucous membranes were pale. The cervical, axillary, inguinal, mediastinal and mesenteric lymph nodes were moderately enlarged. The blood, as it escaped from the various severed vessels, appeared thin and watery. The *heart* was normal except for petechial hemorrhages on the pericardium and endocardium. Both lungs contained small patches of bronchopneumonia and the larger bronchi were filled with a purulent exudate. The *liver* was enlarged, and minute nodules of leukemic infiltration could be seen with ease. The *spleen* weighed 290 gm. It was red, pulpy, and the Malpighian corpuscles appeared enlarged. The kidneys had a combined weight of 380 gm. Scattered throughout the cortex and

medulla of the kidney were numerous small white nodules. The bone marrow in the upper third of the right femur appeared firm, yellowish-white in color, and contained scattered red hyperplastic areas.

*Microscopic Examination.* The representative specimens of lymph nodes from the various chains were stained with eosin and methylene blue, and showed an absence of normal architecture. There was no differentiation between the follicular and medullary portions. No germinal centers could be seen. There was a general overgrowth of tissue by a type of cell slightly larger than the usual lymphocyte, and which contained a thin rim of protoplasm. The nuclei as a rule were round, clear and did not stain as deeply as normal lymphocytes. Some of these cells showed a slight nuclear indentation. Among some of these cells could be seen an occasional one in which the nucleus appeared to be undergoing an amitotic division. Sprinkled in between these cells could be seen numerous red blood cells, and some of these appeared similar to the normoblast.

*Bone-marrow* (Giemsa) showed a moderate number of fat-cells. The interstices between the fat-cells were infiltrated by large numbers of cells similar to those described as seen in the lymph-node. Some of these areas were large and completely obliterated the fatty tissue. Oxydase stain showed very few myelocytes. Only an occasional small focus of red blood cell formation could be identified.

*Heart.* In the pericardial fat there were definite small cellular accumulations, but none in the heart muscle. These cells again were similar to those described above. In the coronary vessels large numbers of leukemic cells could be seen.

*Spleen.* The Malpighian corpuscles were irregular in size and shape, but in general were enlarged. The pulp was markedly increased in cellularity, the predominating cell being the lymphocyte. Among these cells was an occasional nucleus undergoing amitotic division.

*Liver.* There were numerous foci of leukemic infiltrates which were, for the most part, periportal in distribution. There was a considerable amount of hemosiderosis.

*Kidneys.* Small aggregations of leukemic cells were found between the tubules; an occasional cell could be seen undergoing amitotic division.

*Anatomic Diagnosis.* Lymphatic leukemia, chronic. Generalized lymphadenopathy, especially in mediastinal retroperitoneal and mesenteric nodes. Splenomegaly, 290 gm. Leukemic infiltration of liver and kidneys. Petechial hemorrhages in epicardium. Secondary anemia. Bronchopneumonia and purulent bronchitis.

The accompanying microphotographs of actual blood smears and of tissue-sections of lymph nodes and bone-marrow show numerous lymphatic cells in the process of direct nuclear division (amitosis). It will be seen in the accompanying microphotographic figures that this feature of amitosis is particularly striking.

*Benzol and Leukemia.* Three important questions are suggested by a study of the clinical data and autopsy material of this patient:

1. What effect does benzol have on lymphatic tissue?

2. Is it not possible for benzol, like other well known hemopoietic irritants, to upset the hemopoietic balance between cell growth and destruction, giving rise to lymphoid hyperplasia?

3. Does this lymphoid hyperplasia always stop just short of leukemia, or can it, under prolonged irritation or in susceptible individuals, progress to lymphatic leukemia?

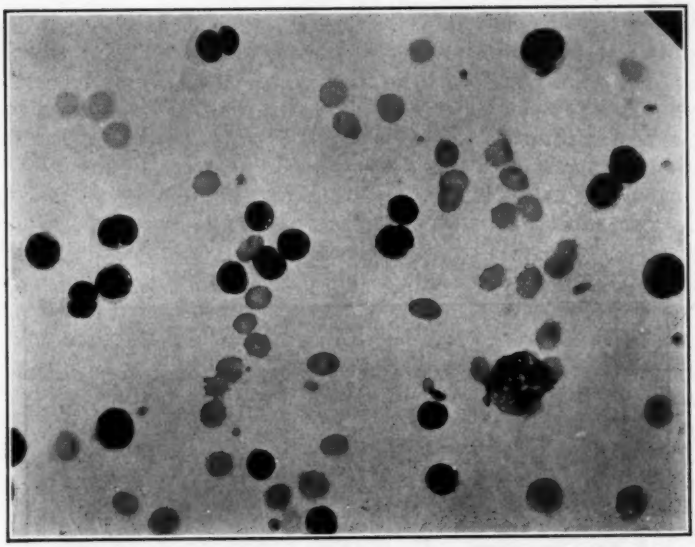


FIG. 1.—Blood film (Jenner-Giemsa stain). Showing direct division of cells.

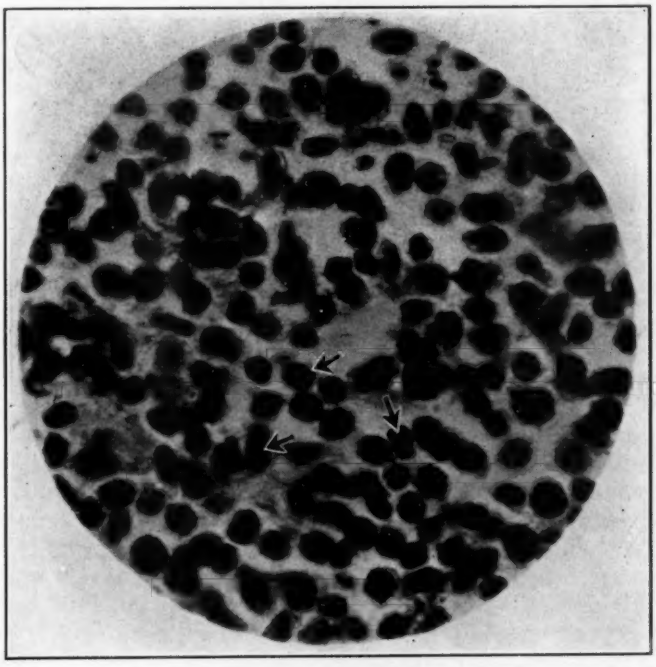


FIG. 2.—Bone marrow.

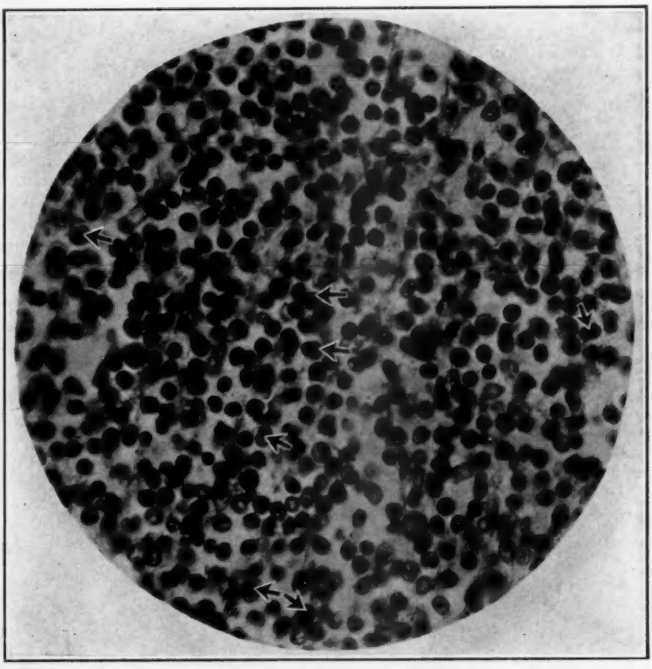


FIG. 3.—Lymph node.

Among the experimental work on the action of benzol on lymphatic tissue, G. O. E. Lignac[2] in 1928 reported the results of injecting mice with from 25 to 30 injections of benzol (0.1 cc. of 0.3 cc. benzol in 10 cc. olive oil). He concluded: "All the symptoms of hyperplasia developed. After a time the spleen, which was at first hypertrophied, decreased in size. No animals showed lymphatic leukemia, only hyperplasia. Up to the present time, I have not succeeded in producing lymphatic leukemia." He further states, "The experiments cited are not numerous but are important in connection with work with leukemia. In the mice the growth is not ordinary hyperplasia, but should be considered as a tumorous growth similar to leukemia. Precursor cells show spontaneous growth from numerous centers, in 1 case breaking the liver capsule. It is a real tumor of precursors of white blood cells. The immature or undifferentiated cells suggest acute leukemia. Development of tumor may, or may not, be accompanied by a leukemic blood picture. No one knows what factors cause an overflow of leukocytes into the blood stream."

In connection with hemopoietic irritants some interesting experimental work by Murphy and Sturm[3] appears to have a bearing. They subjected mice, rats and guinea pigs to dry heat at temperatures of from 55° to 65° C. Short exposures of about 5 minutes were carried out and white counts were made at intervals over a 3 weeks' period. There was an immediate drop in both neutrophils and lymphocytes which averaged about 3000 cells per c.mm. Seven days after the heating, there was an increase of from 5000 to 10,000 cells per c.mm., the increase being almost entirely in the lymphocytes. Fourteen days after heating, the lymphocytes had increased to from 12,000 to 14,000 per c.mm. above the original counts. The neutrophils remained low and did not begin to increase until about 3 weeks after heating. The lymphocytes were still high, but were beginning to drop back toward normal. Both the large and small lymphocytes were healthy-looking, and did not differ in appearance from those of the normal animal. At from 6 to 10 days after heating, several lymphocytes were noted that appeared to be in process of amitotic division. Every stage of this division could be seen. In some instances from 4 to 5 cells in process of division could be seen in one microscopic field. The microphotographs of these cells, accompanying their paper, bear a striking resemblance to the microphotographs showing amitotic division in this article.

Nakahara,[4] investigating the source of lymphocytosis induced by heat, found that the first change in the spleen and the lymph glands was widespread degeneration of the lymphoid elements. Within 48 hours this was followed by activity of the so-called "germinal centers" with an overproduction of lymphocytes, the spleen and lymph glands becoming larger than normal. There was a marked increase of mitotic figures in the lymphocytes of the germinal centers following the general necrosis.

CHART I.

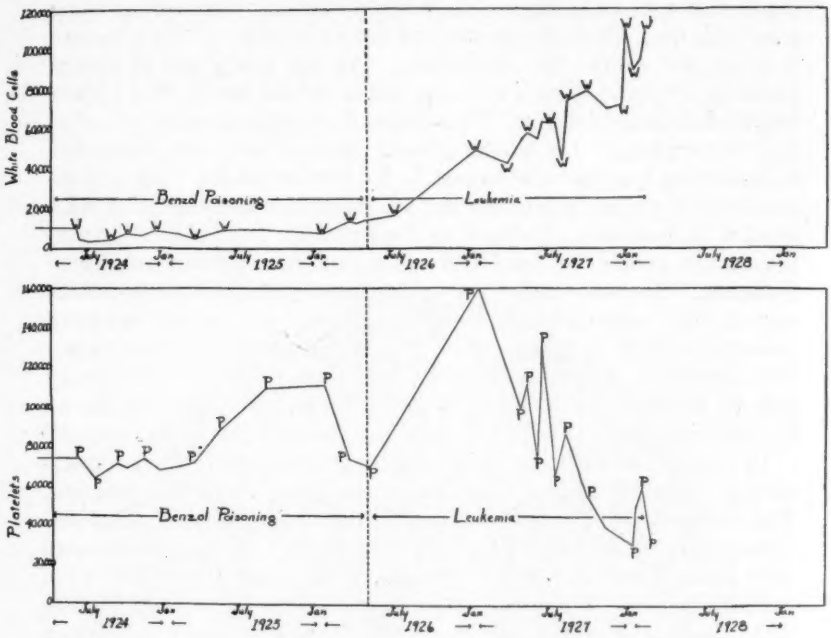
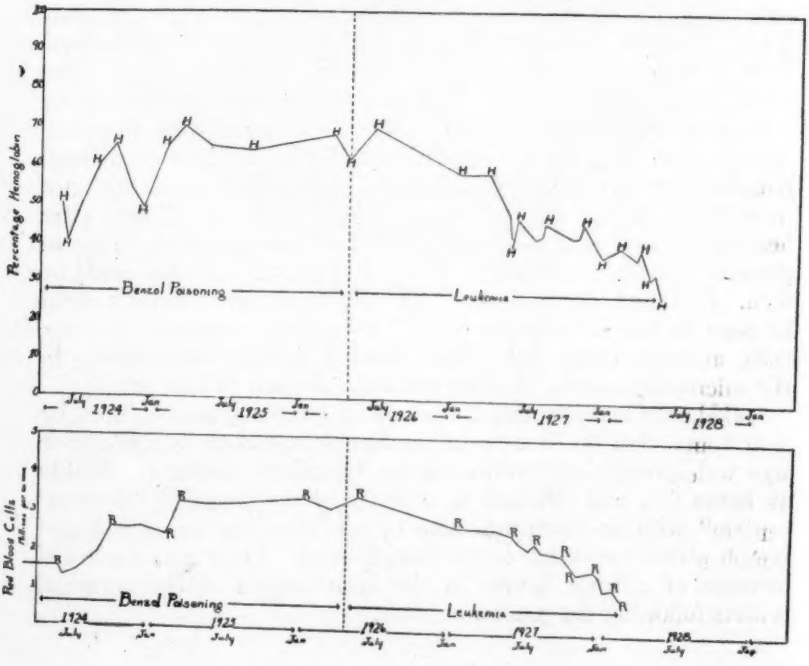



CHART II.



These experiments suggest that benzol may act on lymphatic tissue in a similar manner to dry heat, causing first destruction, then a compensatory hyperplasia, exceeding what we recognize as normal limits. One wonders if under repeated stimuli of this type the balance between orderly production and destruction of lymphocytes might not be upset, resulting eventually in a leukemia. It will be recalled in this connection that Yamagiwa and Itchikawa[5] succeeded in producing tar cancers in rabbits, after other experimenters had failed, by carrying on the chronic irritation over a sufficiently long period of time and by using rabbits instead of less susceptible laboratory animals.

*The Action of Chemicals, Toxins and Radiation on Lymphatic Tissue.* In connection with chemicals, arsenic has long been of interest because of its known power of influencing hemopoietic tissue. Isaacs[6] has studied its effect on red cells, but no mention is made of its action on lymphocytes. He concluded that arsenic acts as a depressor of the bone-marrow causing a decreased production of young red blood cells. When arsenic is stopped, the bone-marrow responds once more with an increase in the rate of maturation of the erythroblastic tissue and an increased production of young red blood cells. In 1929, Baldridge, Rohner and Hausmann,[7] in a report on infectious mononucleosis, mention in their series 6 cases developing a mononucleosis while under antiluetic treatment. In 1925, White[8] reported a severe case of infectious mononucleosis developing under antiluetic treatment. The author, in 1925 (unreported), studied a case presenting a clinical picture of infectious mononucleosis with a severe Vincent's infection of the buccal cavity, developing after neoarsphenamin administered for a luetic infection.

It has been considered by some writers (Farley[9]) that the benzol ring in arsphenamin and its derivatives may be responsible, along with arsenic, for hemopoietic tissue damage. The toxins of certain acute infections have long been considered to be a cause of leukemoid blood-pictures, and some writers, as Sternberg,[10] believe acute leukemia is an infection. Cabot[11] reports leukemoid blood-pictures following lymphangitis, furunculosis, acute streptococcus tonsillitis and cervical adenitis. Herz[12] mentions cases of infection with a blood-picture simulating lymphatic leukemia. Türk (quoted by Herz) believes there is a relationship between "lymphatic reaction" and lymphatic leukemia. Marchand[13] presents a case of severe sepsis with bone-marrow exhaustion, and a picture of lymphoid hyperplasia. This last instance is a situation somewhat comparable to the case under consideration where benzol exhausting the bone-marrow is followed by lymphoid hyperplasia and lymphatic leukemia.

The effect of Roentgen rays and radium on hemopoietic tissue has not as yet been well worked out. This is due to the length of

time necessary and the number of factors, such as dosage and susceptibility, that must be controlled in such experimental work. There are cases reported of leukemia and also of aplastic anemia resembling pernicious anemia in workers exposed to Roentgen ray and radium. Emile-Weil[14] reported 2 cases, engineers working in the same laboratory with radioactive material. One died with pernicious anemia and the other with myelogenous leukemia. He quotes other reports in the literature, mentioning deaths from lymphatic leukemia. Farley,[15] commenting in Medicine (1928) on Emile-Weil's report states, "In view of the undoubted production of aplastic anemia by the action of rays on the bone-marrow, it is not surprising that the production of a myelogenous type of leukemia by rays should be reported, but the production of lymphatic leukemia by such means should not be credited without very close scrutiny."

It seems to me that Farley's comment refers to the action of rays on the bone-marrow, but if radiation of the marrow can bring about aplastic anemia and myelogenous leukemia, it would seem as if these same rays, acting on lymphatic tissue, much more easily influenced by radiation, might produce a lymphatic leukemia. The bone-marrow is only a portion of the hemopoietic system, all portions of which must be closely interdependent. The exact mechanism of the production of a leukemia is unknown in either case. One can speculate that it is chronic irritation applied to cells whose function is that of growth primarily. The response of cells to irritation is division and growth, or death of the cell.

Experimental work carried on at the Rockefeller Institute[16] tends to show that with a certain dose of Roentgen-ray, a lymphocytosis similar to that produced by heat can be brought about. Blood counts after the treatment described show a lymphocyte change characterized by an initial fall, followed by a marked rise.

**Discussion.** The data presented in this case are not regarded as furnishing definite proof that benzol caused the lymphatic leukemia. The suggestion to which the evidence points is that the benzol exposure acted as an irritant and destructive agent to the hemopoietic system, upsetting the balance between lymphocyte production and destruction, resulting in lymphatic leukemia. The action of the benzol in destroying erythropoietic and leukopoietic tissue caused a stimulus for regeneration of these two types of tissue, located chiefly in the bone-marrow. The damaged marrow could only respond to a limited extent, producing a red cell and granulocyte response at a level which remained at first below the former normal level. A considerable stimulus for regeneration must operate on the hemopoietic tissue as a whole in these cases of marrow damage. In an individual with a labile lymphatic apparatus, as this individual under consideration appeared to have, the lymphatic response may be unusual and carry on to a leukemic state. This patient was a short, obese individual, who, at age 58, had hyper-

trophied tonsillar tissue, and looked like the typical, so-called "lymphatic" type. Individual susceptibility must be an important factor in determining the response of hemopoietic tissue to various types of irritative and destructive stimuli.

**Conclusions.** 1. A case of benzol poisoning is presented in which the patient recovered for a time, settling to a new and lower level of blood cell production, then gradually passing into a true, autopsy verified status of lymphatic leukemia with a fatal termination.

2. Instances are drawn from the literature suggesting that benzol, like other agents destructive to hemopoietic tissue, may upset the balance of orderly blood cell production and destruction, bringing about a tissue-environment favorable to the production of lymphatic leukemia.

3. Attention is directed to the presence of direct division of the nucleus, both in many lymphatic cells in the blood stream and in lymphatic tissue cells in lymph nodes and bone-marrow.

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## THE ADVANTAGES OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT IN THE TREATMENT OF PERNICIOUS ANEMIA.

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The desirability of large doses of liver in the treatment of the patient with pernicious anemia as originally advised by Minot and Murphy[1] has become almost universally recognized during 8 years

of use in thousands of patients. The development of a fraction of liver for oral administration by Cohn and his associates[2] has made it possible for many persons to consume adequate amounts with less difficulty than when whole liver is used. Liver fractions and other substitutes for liver, to be ingested, have shown no other advantage than this over the use of whole liver, and are uniformly more expensive to use. The first solution of liver extract prepared for intravenous injection,[3] although potent, was not practical for general use. The development of a concentrated solution for use by intramuscular injection has made the problem of adequate dosage more simple and more certain than it has ever been before.

Early trials, at this hospital, with intramuscular injections of a simple solution of liver extract indicated the practical value of such a method. Following a report[4] of May 26, 1931, concerning one of the earlier cases treated with this extract, observations in a series of 24 patients who had received intramuscular injections were reported.[5] The results obtained in the larger group demonstrated conclusively the important and striking effects anticipated as a result of the preliminary work. These results have also been confirmed in this country by several investigators working independently.[6,7,8,9]

It was obvious that in order to be practical for general use the solution for intramuscular injection must be of such a nature that it could be easily and safely used and of such a concentration and potency that the optimal results should be obtained with the fewest possible injections. This was accomplished by the production of a solution of liver extract of such a concentration that the active substance from 100 gm. of liver was contained in 5 cc. of solution. This preparation,* the first for intramuscular injection to be made available for general use in this country, after acceptance by the Council on Pharmacy and Chemistry of the American Medical Association was further concentrated and certain irritating substances eliminated, so that 3 cc. of solution retained the same potent material as was contained in 5 cc. previously. The potency of this material as determined by its clinical effect may be indicated by comparison with the effect of whole liver, which may best be considered as the standard for potency. It has been estimated from observations made during the maintenance treatment of 81 patients by means of intramuscular injections of Solution of Liver Extract (Lederle) that the contents of a vial (3 cc.) containing active principle from 100 gm. of liver will replace from 30 to 50 times that amount (3000 to 5000 gm.) of whole liver administered by mouth.

The practical efficiency of a concentrated solution of liver extract, when given intramuscularly as observed in the treatment of 101 cases and reported in a previous paper,[10] has led to the following conclusions

* Solution Liver Extract Parenteral—Lederle Laboratories, Inc.

in regard to the advantages of this form of treatment as compared with either the use of whole liver or potent substitutes for administration by mouth or less concentrated solutions for intramuscular use.

1. *Certain Dosage.* The dosage is under absolute control of the physician. Although the treatment may be given by the patient's nurse, the relative infrequency of treatment makes it quite possible and desirable for the physician to do this. In consequence the physician will see the patient at frequent intervals, thereby insuring him of the best results.

2. *Severe Relapse.* Its strikingly rapid effect makes it the treatment of choice for the patient in severe relapse. The first and maximum effects are evident many hours before these effects may be observed following the administration of liver or liver substitutes by mouth. As previously suggested,[5] it may well replace transfusion in the critically ill patient.

3. *"Resistant" cases.* Because of the ease and certainty of administering adequate amounts of effective substance the intramuscular injection of the concentrated solution is particularly valuable for the treatment of the patient in whom it has been found difficult to maintain an essentially normal condition of the blood. This apparent resistance to satisfactory improvement may be due in some instances, when liver or liver extract is given by mouth, to an inability on the part of the patient to obtain, to take or to utilize an adequate amount of the material in liver which is effective in producing blood.

4. *Combined System Disease.* Since control of the conditions associated with spinal cord or peripheral nerve damage depends primarily upon the utilization of optimal amounts of the active substance in liver, the concentrated solution given intramuscularly is the treatment of choice.

5. *Uncomplicated Pernicious Anemia.* For the patient with uncomplicated pernicious anemia the routine maintenance treatment with intramuscular injections of the concentrated solution of liver extract is an ideal method. The certainty of dosage and the convenience of its use, because of the relative infrequency of administration in this group particularly, is generally appealing to the patient. It has been found[10] that optimal results are to be obtained by injections of the contents of a vial (3 cc.) at intervals varying from 1 to 6 weeks, the average interval being 3 to 4 weeks. The use of intramuscular treatment does not contraindicate a subsequent return to peroral therapy if this be desired.

6. *Economy.* The saving possible through the use of this method of treatment is of especial interest to those patients who must continue treatment throughout life. Not only is the cost of material small in comparison with that of liver or its substitutes for oral use, as previously shown,[5] but also a saving is almost always pos-

sible, even including the expense of injection. This saving is particularly noticeable with the use of the concentrated solution described by the author,[5] because of the low cost of the material and the relative infrequency of injection as compared with less concentrated solutions.

7. *Travel.* It is often difficult for the patient travelling to be certain to obtain good liver along the route and the substitutes for ingestion are bulky to carry. Intensive intramuscular therapy prior to the trip will be sufficient for several weeks without further treatment, or a few vials may be easily carried and injected as desired en route.

8. *Mode of Administration.* That the solution must be administered by needle may be considered as a minor disadvantage of this form of treatment compared with peroral therapy, although the relative infrequency of injections made possible through concentration of the solution has minimized this disadvantage.

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## CONGENITAL AORTICOVENTRICULAR FISTULA WITH ENGRAFTED ACUTE SUPPURATIVE ENDOCARDITIS.*

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Communications between the aorta and the right ventricle are rare. The majority reported have been aneurysms of the aortic septum, rupturing into the right ventricle. But 3 cases have been reported of a congenital communication between the aorta and the right ventricle. These are:

* Read before the New York Pathological Society, December 10, 1931, and the Brooklyn Pediatric Society, March 22, 1931.

Rickards,[1] male, aged 30. The right and left anterior aortic valves were congenitally fused. Behind the right half was a large round orifice, with smooth, membranous, funnel-shaped wall, opening into the right ventricle, between healthy pulmonary cusps. Immediately below the same cusp was a circular aperture in the septum with smooth, membranous wall, passing into the conus of the right ventricle.

Charteris,[2] male, aged 53. Immediately behind the right aortic valve was a rounded opening with firm margin leading into the right ventricle. A patch of endocardial thickening was present on the opposite wall of the right ventricle.

Livingston,[3] male, aged 4 months. The aortic valve was bicuspid, the heart was enlarged. At the commencement of the aorta, a communication led into the right heart, opening above and below the tricuspid valve, and partially closed by a part of this valve.

To these we wish to add a fourth case.

**Case Report.** A. M., male, white child, aged 1½, was hospitalized on January 30, 1931, with complaints of fever, weakness and irritability.

*Past History.* Patient was a normal, spontaneous, full-term baby. The patient had "frequent attacks of tonsillitis," and had an attack of "grippe" 2 weeks prior to the present illness. There was no history of dyspnea nor cyanosis.

*Present Illness.* The present illness began 4 days prior to hospitalization with joint pains and pyrexia ranging from 103° to 106°. Acute rheumatic fever was diagnosed and hospitalization ordered.

Examination revealed a very pale and markedly dyspneic male infant. The tonsils were congested, the lungs, abdomen and extremities were negative. The knees and elbow joints only were painful, particularly on motion. There was no redness, heat or swelling.

The heart was enlarged to the right and left. A soft systolic blow, localized to the apex, was present. At the midsternum there was a loud, harsh, flapping-to-and-fro murmur. A rough systolic murmur was present at the pulmonic area, transmitted upward to the left. The second pulmonic sound was not heard. The temperature was 105°; pulse 160 and weak.

Blood count: red blood cells, 3,100,000; hemoglobin, 60 per cent; white blood cells, 23,000; differential: 87 per cent polymorphonuclears; 13 per cent lymphocytes.

Roentgenologic examination revealed an enlarged cardiac shadow. The child's condition rapidly became worse and he died on the following morning.

The blood culture revealed streptococcus hemolyticus, beta type.

*Autopsy Protocol.* Autopsy was performed 2 hours postmortem.

The body was that of a well-nourished and developed white male child, weighing 28 pounds, and 36 inches long. The skin and the conjunctivæ were extremely pale; the lips and finger tips were pale and cyanosed. No petechiæ nor hemorrhages were present anywhere.

The pericardium was not adherent to the pleura. The parietal pericardium was dulled, gray and loosely adherent to the visceral layer in 2 places. One area, 1.2 cm. in diameter, was situated on the anterior surface of the left ventricle at its midportion just lateral to the anterior descending branch of the left coronary artery. The other area was 2.5 cm. in diameter, irregularly circular in outline,

and was situated over the base of the pulmonary and aortic conus and the adjacent anterolateral wall of the right ventricle. No free fluid nor blood was present in the pericardial cavity. The left ventricle was moderately hypertrophied, the left auricle was slightly hypertrophied and dilated. The tricuspid, mitral and pulmonic leaflets were intact. The endocardium of all the chambers, except as stated hereafter was smooth and glistening.

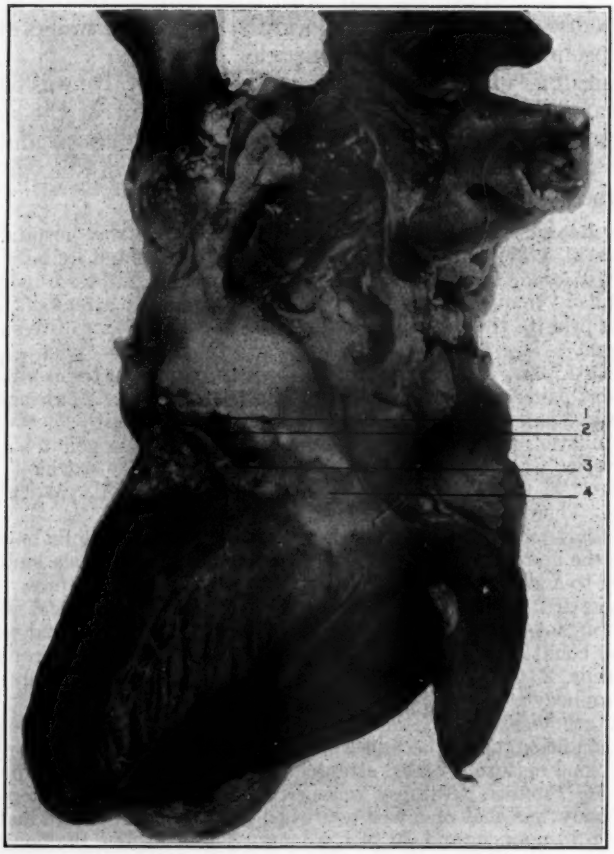


FIG. 1.—Heart opened exposing left ventricle and aorta to show bifid aortic valve and aortic opening of fistula. (1) Coronary orifices; (2) aortic opening of aortico-ventricular fistula containing thrombus; (3) anterior aortic valve cusp; (4) posterior aortic valve cusp.

The aortic valve was composed of two cusps, a normal-sized posterior, and an anterior approximately twice the length of the former (Fig. 1). Midway along this cusp was a slight longitudinal bulge of the anterior aortic wall forming a faint ridge, extending into the

sinus of Valsalva, resembling a very imperfect and rudimentary right-left commissure. This anterior cusp was diffusely thickened, firm, and opaque white; its free edge, smooth and covered by an apparently intact endocardium, was somewhat gouged posteriorly; the sinus of Valsalva narrowed here. Both coronary orifices appeared to enter into the same sinus.

Between these orifices was a round aperture 0.6 cm. in diameter and on the same level with them. The edges of this orifice were thickened, indurated and smooth except along the upper border, where there was slight ulceration. This opening led into a fistulous tract which extended through the aorticopulmonary septum, obliquely downward, forward and to the right, to open into the right ventricular cavity immediately beneath the commissure between the right and left posterior pulmonic valve cusps and just below the level of attachment of these cusps. The commissure was slightly widened, the cusps pushed somewhat apart (Fig. 2). This tract narrowed progressively from aorta ventricleward. The lumen of the tract was filled with soft, gray-yellow thrombus, a portion of which projected through the aortic opening into the aortic lumen; the aortic end of the tract was only partially filled with the thrombus. At the ventricular end the thrombus was very firmly adherent to the tract wall; at the aortic end it was a bit more loosely attached. The ventricular opening of the tract had a ragged edge; to the occluding thrombotic material was attached a narrow bit of fibrin which spread onto the ventricular endocardium for about a millimeter in all directions.

Communicating with the tract was an irregular triangular cavity in the posterolateral wall of the right ventricle, 1.2 cm. in length, about 0.4 cm. wide at its base (valveward) and occupying nearly the entire thickness of the wall. This area bulged slightly into the ventricular cavity. The overlying endocardium was dulled; there was no gross ulceration of the endocardium and no attached thrombi.

One-half centimeter distal to the origin of the left subclavian artery, the aorta, previously 2 cm. in diameter, narrowed to 1.4 cm. in diameter for a distance of 0.6 cm., again to become 2 cm. wide more distally.

The foramen ovale and the ductus Botalli were completely occluded.

The kidneys showed a diffuse cloudy swelling and numerous, minute abscesses. The spleen was of the red splenic tumor type. The liver showed a diffuse cloudy swelling. The other organs showed no gross changes.

*Microscopic Examination.* The sections of the fistulous area were composed of peripheral zone of cardiac musculature, central to which was a zone of granulation tissue bordering the lumen of the tract. The lumen contained granular, amorphous fibrinous débris and leukocytes. Through this central zone, and in the adja-

cent portion of the granulation tissue zone, were numerous clumps of short-chain streptococci. In the more peripheral portions of the granulation tissue zone were dense collagenous fibers and fragments of atrophic cardiac muscle. The remainder of this zone was composed of fibroblasts, young connective tissue cells, fine fibrillary

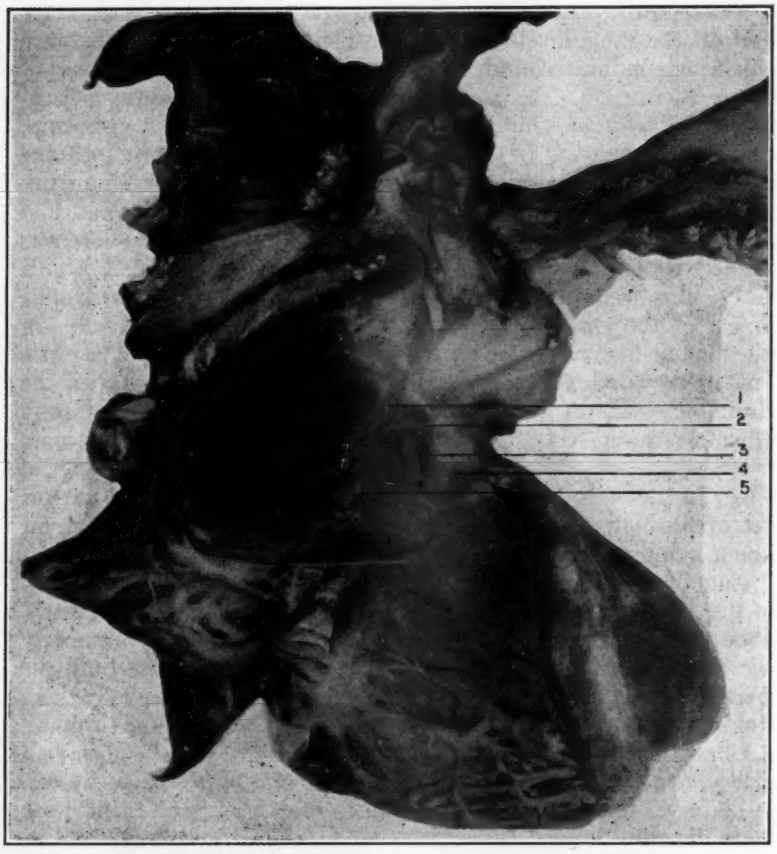


FIG. 2.—Heart opened exposing right ventricle to show ventricular opening of fistula between and below posterior pulmonary valve cusps. The intramyocardial abscess appears as a slight bulge directly below the opening of the fistula; the widened commissure is directly above it. (1) Right posterior pulmonary valve cusp; (2) right-left pulmonary commissure; (3) ventricular opening of fistula; (4) left posterior pulmonary valve cusp; (5) bulge of intracardiac abscess.

connective tissue and numerous capillaries. The entire zone was sparsely infiltrated with polymorphonuclear leukocytes, and lymphocytes, the cellular infiltration becoming denser centrally.

In the sections taken through the ventricular end, the granulation tissue zone was wider, the adult fibrous tissue greater in amount

than in those from the aortic end. In these sections, as well as in the sections through the cardiac wall abscess, the myocardium was diffusely infiltrated with polymorphonuclear leukocytes, the infiltration becoming less marked as one passed away from these areas. In sections through the aortic end, no myocardial cellular infiltration was present nor was any present in sections through various portions of the heart away from the tract.

The kidneys contained discrete abscesses. The liver and kidneys showed diffuse cloudy swelling. The splenic sinuses and pulp showed a marked acute congestion.

**Discussion.** Two possible modes of formation of the tract described, must be considered. Either it is congenital or the tract is the result of ulceration of the septum by the infectious process. It seems to us that the former is the more likely explanation.

Grossly and histologically, the evidence points to the fistula as one of long duration, apparently antedating the recent necrotizing process. The aortic end of the fistula is markedly thickened, and except for a very small ulcerated area, its lining is smooth. This end of the tract is covered by swollen, but otherwise intact, endothelial cells. No signs of an inflammatory process are apparent in the wall of the tract in sections through the aortic end, a finding to be expected if the fistula were the result of an inflammatory ulcerative process.

Further, the central infected and necrotic areas within the fistula are separated from the myocardial wall of the tract by a zone of organizing granulation tissue. In the more peripheral portions of this zone, adult collagenous connective tissue fibers are present. The inflammatory cellular exudate is present only in the centralmost portion of the thrombus. As the periphery of the thrombus is approached, the cellular content becomes much less marked, while the zone adjacent to the myocardial wall contains only an occasional wandering cell and no organisms. The myocardium lining the tract shows no cellular infiltration. The only point at which the myocardium is invaded is the right ventricular wall abscess, which is in direct continuity with the ventricular end of the fistulous tract. At this point the fistula is narrowest, and here the bacterial and cellular content of the contained thrombus is greatest. These findings suggest a previous fibrin deposition, sterile thrombus formation and subsequent organization of the thrombus within the fistula. This apparently preceded the acute necrotizing process which is of more recent development and without, as yet, any evidence of organization (healing).

A comparison of the degree of fibrin layering and organization in various portions of the fistula is of considerable importance. Examination of the sections showed the most organized fibrin and the greatest amount of adult collagen near the ventricular end of the tract. This point, contiguous with the myocardial abscess, showed

the greatest amount of inflammatory reaction centrally. If the fistula were purely of inflammatory origin, the smallest degree of organization of the thrombus is to be expected at this point; whereas the appearances are quite compatible if the tract antedated the acute inflammatory process.

The absence of an endothelial lining along the tract wall does not militate against the theory of a congenital origin. The tract narrowed progressively toward the ventricle, and sterile thrombus formation seems to have proceeded from this point, the probable site of greatest blood puddling, toward the aorta. In time, the entire wall was covered by thrombus, the underlying endothelium probably being destroyed in the process. That the process was not complete is evidenced by the presence of an endothelial lining in the

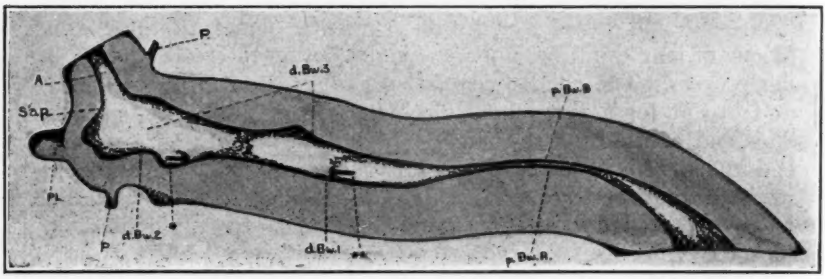


FIG. 3.—Left half of model by Julius Tandler of the bulbus cordis of the Embryo H6, divided longitudinally. *A*, aorta (4 aortic arch); *d.Bw.* 1–3, distal bulbar swelling; *p*, attachment of pericardium; *p.Bw A–B*, proximal bulbar swelling *A* and *B*; *PL*, pulmonary artery (6th aortic arch); *S.a.p.*, septum aortopulmonale; *, point at which the sound in the lumen of the pulmonary artery disappears, being covered by the fusion of the distal bulbar swellings 1 and 3, forming distal bulbar septum; **, point at which the sound again appears in the common lumen. The subdivision of the common efferent tube is produced distally by the septum aortopulmonale, in the middle region by the distal bulbar septum and proximally by the proximal bulbar septum. Between these three portions of the partition there are two points of communication, in which the ends of the sounds are visible. (From Keibel and Mall, Embryology, vol. **2**, Fig. 384, p. 552.)

sections through the aortic end of the tract, where thrombus was not in contiguity with the wall.

To explain the congenital defect found in this case, it will be necessary to review briefly the embryologic mechanism involved in the formation of the septum dividing the aorta and pulmonary artery.[4,5]

Three factors take place in the subdivision of the efferent tube:

1. The proximal bulbar swellings;
2. The distal bulbar swellings;
3. Septum aortopulmonale.

The proximal bulbar swellings consist of two endocardial thickenings in the proximal portion of the bulbus (Fig. 3). Swelling A, beginning distally on the left posterior wall, passes to the left,

finally to disappear proximally on the right anterior bulbar wall. Swelling B begins distally on the anterior wall and passes thence over the right wall to disappear proximally on the posterior bulbar wall, on the same level as Swelling A, at the junction of the bulbus and the ventricle. At a later stage A and B fuse to form the proximal septum.

A series of swellings are now developed in the distal half of the bulb but they do not present the regularity of form and occurrence that obtains in birds and reptiles. These distal swellings are 4 in number. Starting with the right distal one and proceeding to the left and backward they are denoted by the numbers 1 to 4. When followed proximally, they are seen to run downward on the bulbar wall in a clockwise spiral. Swellings 1 and 3 are strongly developed while 2 and 4 are weaker. Swelling 1 lies distally on the right wall of the bulbus and passes gradually backward and to the left, joining Swelling A at a later stage. Swelling 3 begins above on the left wall and passes to the right anterior one as it descends, later joining Swelling B. Eventually, 1 and 3 fuse to form the distal septum. Swellings 2 and 4 have a position between Swellings 1 and 3, Swelling 2 passing from above and behind downward into the left, and Swelling 4 from above and in front, downward to the right.

The septum aortopulmonale arises as a partition between the sixth and fourth pairs of aortic arches, grows proximally and extends into the efferent tube, dividing it distally into aorta and pulmonary artery.

At this stage the three portions making up the septum are still distinctly separated. The aorta and pulmonary artery are still in communication at three points, viz.:

1. Between the aortopulmonale septum and the distal end of the distal bulbar swellings.
2. Between the proximal end of the distal bulbar swelling and the distal end of the proximal bulbar Swellings A and B, and
3. Proximal to the proximal bulbar Swellings A and B.

Normally, after the formation of the septum, the aortic side contains one-half of each Swelling 1 and 3 and all of Swelling 4, and the pulmonic side the other halves of Swellings 1 and 3, and all of Swelling 2. The most proximal portions of these swellings hollow out on their distal slopes, forming the anlage of the semilunar valves.

We can explain our defect in one of two ways:

1. The proximal and distal septa fuse and the aortic valves form from their half of the proximal portions of the distal bulbar swellings. The communication between the distal bulbar septum and the septum aortopulmonale remains patent and the pulmonic valves form from the proximal end of the septum aortopulmonale.

2. Or else, since the distal bulbar swellings are often irregular as to form and occurrence, we can conceive of a persistent communication in the distal bulbar septum itself, immediately distal to the

aortic valves, and the pulmonic valves arising immediately distal to such a defect.

Of great importance in connection with a congenital origin of the tract is the relative position of the aortic and pulmonic valve cusps in this case. Measured from the anterior end of the apex at a point exactly midway between the left and right surfaces of the interventricular septum, these valves rose at points 5.9 cm. and 6.7 cm. respectively, a difference of 0.8 cm. Similar measurements of 20 hearts from children of the same age, in whom no cardiac or aortic anomalies or pathologic changes were present disclosed a difference of not more than 0.2 cm., with the variation of distance greater for the aortic valve in 12 instances and for the pulmonary valve in 8 instances. The difference noted in this case suggests that the direction of the fistula was influenced by an abnormally high origin of the pulmonary valve cusps, above the level of origin of the aortic cusp, both probably arising from the distal bulbar septum.

**Summary.** 1. A case is presented of an acute bacterial infection superimposed upon a heart containing a fistula between aorta and right ventricle and a bicuspid aortic valve and coarctation of the aorta.

2. An explanation is offered for the presence of the fistula.

Dr. Maude Abbott, to whom the evidence was submitted has concurred with this explanation. (See Nelson Loose-leaf article, 1932 continuation, p. 272).

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## SERIAL NON-PROTEIN NITROGEN STUDIES AND THEIR PROGNOSTIC SIGNIFICANCE IN ACUTE CORONARY OCCLUSION.

### A PRELIMINARY REPORT.*

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CORONARY occlusion, a clinical entity that was first described by Herrick in 1912,[1] has become one of the most interesting diseases that the general practitioner and internist see today. Heberden[2] in 1768 first described angina pectoris, a condition with which

* Submitted for publication January 26, 1933.

coronary occlusion is closely associated and often confused. Jenner[3] first associated angina pectoris with diseases of the coronary arteries.†

"When you are acquainted with my motives, I presume you will pardon the liberty I take in addressing you. I am prompted to it from a knowledge of the mutual regard that subsists between you and my worthy friend Mr. Hunter. When I had the pleasure of seeing him at Bath last autumn, I thought he was affected with many symptoms of the angina pectoris. The dissections (as far as I have seen) of those who have died of it, throw but little light upon the subject. Though in the course of my practice I have seen many fall victims to this dreadful disease, yet I have only had two opportunities of an examination after death. In the first of these I found no material disease of the heart, except that the coronary artery appeared thickened.

"As no notice had been taken of such a circumstance by anybody who had written on the subject, I concluded that we must seek for other causes as productive of the disease: but about 3 weeks ago, Mr. Paytherus, a surgeon at Ross, in Herefordshire, desired me to examine with him the heart of a person who had died of angina pectoris a few days before. Here we found the same appearance of the coronary arteries as in the former case. But what I had taken to be an ossification of the vessel itself, Mr. P. discovered to be a kind of firm fleshy tube, formed within the vessel, with a considerable quantity of ossific matter dispersed irregularly through it. This tube did not appear to have any vascular connection with the coats of the artery, but seemed to lie merely in simple contact with it.

"As the heart, I believe, in every subject that has died of the angina pectoris, has been found extremely loaded with fat; and as these vessels lie quite concealed in that substance, is it possible this appearance may have been overlooked? The importance of the coronary arteries, and how much the heart must suffer from their not being able duly to perform their functions (we cannot be surprised at the painful spasms) is a subject I need not enlarge upon, therefore shall only just remark that it is possible that all the symptoms may arise from this one circumstance.

"As I frequently write to Mr. H. I have been some time in hesitation respecting the propriety of communicating the matter to him, and should be exceedingly thankful to you, Sir, for your advice upon the subject. Should it be admitted that this is the cause of the disease, I fear the medical world may seek in vain for a remedy, and I am fearful (if Mr. H. should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery."

In coronary occlusion we may find a typical history and physical findings such as we find in typical lobar pneumonia, or again it may be as confusing as any atypical pneumonia. The sequence of events—(1) pressing or crushing pain in the region of the precordium (the pain radiating down left arm or up the left side of the neck); (2) a fall in blood pressure; (3) dyspnea associated with cyanosis or ashy-gray appearance; (4) fever and leukocytosis; (5) precordial friction rub—has become well known to many.

There is, however, one point or factor which I believe needs emphasis, and that is the function of the kidney in this disease. We all know that a certain pressure is needed in the arterial system

† As this letter (written year 1778) is not easily available it is given herewith.

for the kidney to carry on its normal function. In fact we even say that in essential hypertension the elevated blood pressure is a safety mechanism so that the vital renal function may be performed, and we know that this is given as one argument for not lowering the blood pressure in these individuals. My observations in acute coronary occlusion do not coincide with this thought. As shown by Cases 15 and 16, the drop in blood pressure and a definite and marked diminution in urinary output are not sufficient in themselves to account for the non-protein nitrogen factor in acute coronary occlusion; for, although both of these cases had a decided and marked drop in blood pressure and a diminution in urinary output, the non-protein nitrogen did not become markedly elevated.

TABLE 1.—CASES 15 AND 16 ILLUSTRATING DROP IN BLOOD PRESSURE AND DIMINUTION IN URINARY OUTPUT. (NOTE NON-PROTEIN STUDIES IN TABLE 2, CASE 16.)

| Case 15. | Blood pressure. | Date. | Fluid intake, cc. | Urinary output, cc. |
|---|---|---|---|---|
| S. S. | 150/90 | 10-14-32 | None recorded | |
| | 105/75 | 10-15 | " | |
| | 74/56 | 10-16 | " | |
| | 108/70 | 10-17 | " | |
| | 102/70 | 10-18 | 3420 | 1320 |
| | 90/70 | 10-19 | 1770 | 500 |
| | 120-80 | 10-25 | 1970 | 840 |
| | 118/90 | 11- 1 | 1960 | 1560 |
| Case 16. | 130/84 | 11-14 | 1300 | 900 |
| C. B. | 140/90 | 1-14-33 (9.00 A.M.) | | |
| | 110/80 | 1-14 (7.20 P.M.) | | |
| | 100/80 | 1-15 | 2490 | 500 |
| | 88/65 | 1-16 (Fibrillating) | 2950 | 400 |
| | 85/60 | 1-19 (Normal rhythm; quinidin) | 1100 | 650 |
| | 75/55 | 1-20 | 2300 | 1100 |
| | 85/60 | 1-21 | 1830 | 880 |
| | 70/45 | 1-23 | 2150 | 600 |

My particular observation concerns the retention of non-protein nitrogen in the blood plasma in 16 cases of coronary occlusion (Table 2).

An analysis of this tabular study indicates that 9 out of the 16 cases showed a non-protein nitrogen retention that was above 40 mg. per 100 cc. (1 had 40 mg.). Of the 6 fatal cases in this group, only 1 showed a non-protein nitrogen below 40. The 3 cases that showed progression or retention of waste products in the blood stream or continued elevation without necessarily progression in amount of non-protein nitrogen terminated fatally. Three individuals in whom serial non-protein nitrogen studies were made and who showed a definite tendency toward lowering of the non-protein nitrogen value recovered. None of the autopsied cases showed evidence of any marked nephritis.

**Summary.** 1. Sixteen cases of coronary occlusion are presented with special reference to the retention of non-protein nitrogen as a prognostic factor.

TABLE 2.—TABULAR STUDY OF 16 CASES OF CORONARY OCCLUSION.

| Name. | Age. | Dates of attack. | Non-protein nitrogen (mg. per 100 cc.). | Kidney function test. | Urine. |
|---|---|---|---|---|---|
| 1. J. B. | 64 | Day of admission, 3/24/32 | 48—3/28/32 | None | 3/25/32: sp. gr. 1820; f. tr. alb. |
| 2. S. A. | 68 | July, 1930 | 46—1/22/31 (Creatinin 3.2) | None | 1/29/31; 2 plus alb.; sp. gr. 1022; no casts. |
| 3. P. D. | 49 | Day of admission, 2/26/31 | 75—2/28/31 (Creatinin 3.5) 30—3/16/31 | None | 2/27/32: sp. gr. 1021. |
| 4. S. L. | 58 | No history of pain; entered 1/26/31 in coma; diabetic. | 32—1/26/31 | None | 1/26/31: 4 plus sugar; neg. acetone; diacetic plus. |
| 5. G. H. | 58 | Attack, 4/11/31 | 37—4/17/31 | None | 4/17/31: sp. gr. 1020; ft. tr. alb. |
| 6. C. P. | 58 | Attack, June 1931; too numerous to count after admission 8/1/31 | 71—8/ 3/31 95—8/ 7/31 133—8/10/31 185—8/11/31 215—8/14/31 | None | 8/3/31: sp. gr. 1026; alb. plus; 8/7/31: sp. gr. 1021; tr. 5 to 6 casts; 8/14/31: sp. gr. 1012; alb. plus; 3 to 4 casts; few red blood cells. |
| 7. A. G. | 51 | 9 attacks since 1912; last attack 8/15/31, on day of admission | 30—8/17/31 | P.S.P. 57%; 9/4/31; Mosenthal negative 9/6/31 | Neg. |
| 8. M. McM. | 66 | First attack 9/4/31; 3 attacks, last 9/9-/31, 9/10/31; admitted 9/9/31 | 33—9/10/31 | None | 9/10/31: sp. gr. 1022; plus alb.; occas. R.B.C.; no casts; 9/20-/31; sp. gr. 1018; alb. neg. |
| 9. J. T. | 56 | Attack Sept. 1931; admitted 11/23/31 | 42—11/24/31 | None | 11/24/31: sp. gr. 1026; sugar pos.; 12/5/31: sp. gr. 1010; neg.; 12/26/31: ft. tr. alb.; sp. gr. 1012; neg. |
| 10. H. DeW. | 60 | July 1931 and 11/21-/31; admitted 11/-26/31 | 110—11/27/31 42—11/30/31 38—12/ 4/31 | None | 11/27/31: sp. gr. 1025; ft. tr. alb.; 11/29/31: sp. gr. 1029; neg. |
| 11. A. P. | 42 | Oct. 1931; admitted 12/9/31 | 34—12/10/31 | P.S.P. 34%, 2 hrs. intraven.; Mosenthal fixed high gravity, 12/14/31 | 12/10/31: sp. gr. 1025; tr. alb.; 12/11/31: neg.; sp. gr. 1020. |
| 12. B. W. | 49 | Mar. 1930; 3 attacks since; last attack 3/5/32; admitted 3/6/32 | 41—3/ 6/32 40—3/ 9/32 142—3/28/32 | None | 3/4/32: neg.; sp. gr. 1031; 3/18/32: neg.: 3/26/32: neg. |
| 13. A. M. B. | 65 | Nov. 1931 to April 24, 1932; 5 attacks | 60—4/30/32 47—5/ 3/32 40—5/10/32 54—6/10/32 | P.S.P. 10%, 2 hrs. | 4/30/32: neg.; 5/17/32: neg. |
| 14. L. M. | 55 | March 1932 | 40—8/9/32 | None | 8/10/32: neg.; sp. gr. 1010. |
| 15. S. S. | 48 | Early part of Sept. 1932, first attack; sev'r'l attacks since; worst 11/21/32 | 29—10/18/32 45—11/ 5/32 27—11/14/32 | P.S.P. 85%, 10/18-/32, 2 hrs. intrav. | Neg. on 3 occasions. |
| 16. C. B. | 58 | Day of admission 1/14/33 | 39—1/16/33 35—1/20/33 34—1/23/33 | P.S.P. 65%, 1/23/33 | Neg. except 1 plus alb., 1/23/33. |

TABLE 3.—ELECTROCARDIOGRAMS OF CASES OF ACUTE CORONARY OCCLUSION.

| | Electrocardiograms. | Outcome. |
|---|---|---|
| 1. J. B. | 3/25/32. A. Auricular fibrillation. B. Left ventricular preponderance. C. Freq. ventricular premature contractions. D. Slurring and notching of *Q–R–S* complexes in Leads II and III. | No death. |
| 2. S. A. | 1/29/31. A. Low voltage, all 3 leads. B. Slurred *Q–R–S* complexes, all 3 leads. C. Ill-defined *T* waves in all 3 leads. | Autopsy proved. |
| 3. P. D. | 2/6/31. A. Auricular fibrillation. B. Slurred *Q–R–S* complexes in all 3 leads. C. Notched *Q–R–S* complexes in Lead III. D. Diphasic *T* waves in Leads I and II; inverted *T* waves in Lead III. | No death. |
| 4. S. L. | None. | Autopsy 1/27/31; coronary occlusion. |

TABLE 3.—*Continued.*

| Electrocardiograms. | Outcome. |
|---|---|
| 5. G. H. 4/22/31.<br>A. Slurred *Q–R–S* complexes in all 3 leads.<br>B. Left ventricular preponderance.<br>C. High take-off of the *T* waves in Leads I and II. | No death. |
| 6. C. P. 8/8/31.<br>A. Slurred and notched *Q–R–S* complexes in all 3 leads.<br>B. Deep *Q* wave in Lead III. | Autopsy 8/15/31; coronary occlusion; few small anemic infarcts in kidneys. |
| 7. A. G. 8/26/31.<br>A. Slight sinus arrhythmia.<br>B. Neg. *T* waves in Leads II and III, with high *T* wave take-off. | No death; diag. chronic nephritis March, 1929; Brooklyn Navy Hosp.; gross anasarca, ++ alb.; urine, occasional R.B.C.; no casts; no blood chemistry done. Mosenthal, negative. |
| 8. M. McM. 9/10/31.<br>A. Sinus tachycardia; neg. *T* waves in Lead I; high take-off of *T* wave in Lead I.<br>B. Left ventricular preponderance. | No death. |
| 9. J. T. 11/28/31.<br>A. Sinus tachycardia; iso-electric or neg. *T* waves in all 3 leads. | No death. |
| 10. H. DeW. 11/28/31.<br>A. Sinus tachycardia; slight sinus arrhythmia; left ventricular preponderance.<br>B. Slurred or notched *Q–R–S* complexes in all 3 leads; iso-electric or diphasic *T* waves in all 3 leads. | No death. |
| 11. A. P. 12/14/31.<br>A. Slight sinus arrhythmia.<br>B. Marked left ventricular preponderance.<br>C. Notched *Q–R–S* complexes in Leads I and III.<br>D. Neg. *T* waves in Lead I. | No death. |
| 12. B. W. 3/7/32.<br>A. Low voltage slurred *Q–R–S* complexes in Leads I and III; poorly defined *T* waves in all 3 leads; freq. ventricular premature contraction. | Autopsy, 4/1/32; coronary occlusion; kidneys neg. except mild arteriosclerosis. |
| 3/15/32.<br>A. Low voltage complexes; right ventricular preponderance.<br>B. Sinus tachycardia; slight sinus arrhythmia. | |
| 13. A. M. G. 5/7/32.<br>A. Left ventricular preponderance; freq. ventricular premature contractions.<br>B. Low voltage, slurring and notching of *Q–R–S* complexes in all 3 leads. | Discharged; edema, etc., increasing. |
| 14. L. M.<br>None. | Died, 8/14/32; autopsy, coronary occlusion. |
| 15. S. S. 10/17/32.<br>A. Slurred *Q–R–S* complexes in all 3 leads.<br>B. Inverted *T* waves, Leads II and III.<br>C. Deep *Q*-III. | |
| 10/22/32.<br>A. Sinus tachycardia.<br>B. Slight sinus arrhythmia.<br>C. Slurred *Q–R–S* complexes in all 3 leads; inverted *T* wave in Leads II and III.<br>D. Deep *Q*-III. | Recovery. |
| 16. C. B. 1/17/33.<br>Slurred and notched *Q–R–S* complexes, Lead I; poorly defined *T* waves, Lead I; diphasic *T* waves, Lead II. | Good, 1/24/33—day of writing. |

TABLE 4.—FATAL CASES SHOWING PROGRESSION OR CONTINUED EVALUATION OF NON-PROTEIN NITROGEN.

| Name. | Age. | Dates of attack. | Admission. | Non-protein N (mg. per 100 cc.). |
|---|---|---|---|---|
| C. P. | 58 | June, 1931; then too numerous to count | 8/1/31 | 71—8/ 3/31<br>95—8/ 7<br>133—8/10<br>185—8/11<br>215—8/14 |
| B. W. | 49 | March, 1930; 3 attacks since 3/5/32 | 3/6/32 | 41—3/ 7/32<br>40—3/ 9<br>142—3/28 |
| A. M. B. | 65 | November, 1931 to April, 1932, 5 attacks | | 60—4/30/32<br>47—5/ 3<br>40—5/10<br>54—6/10 |

TABLE 5.—RECOVERED CASES SHOWING RETROGRESSION OF NON-PROTEIN NITROGEN.

| Name. | Age. | Dates of attack. | Admission. | Non-protein N (mg. per 100 cc.). |
|---|---|---|---|---|
| P. D. | 49 | .... | 2/26/31 | 75— 2/28/31<br>(Creat., 3.5)<br>30— 3/16 |
| H. DeW. | 60 | July and November, 1931 | 11/26/31 | 110—11/27/31<br>42—11/30<br>38—12/ 4 |
| S. S. | 48 | Early part of September, 1932 first attack; several attacks since; worst 11/21/32 | | 29—10/18/32<br>45—11/ 5<br>27—11/14 |

TABLE 6.—GROUP SHOWING ELEVATED NON-PROTEIN NITROGEN STUDIES IN ACUTE CORONARY OCCLUSION.

| Name. | Age. | Dates of attack. | Admission. | Non-protein N (mg. per 100 cc.). |
|---|---|---|---|---|
| P. D. | 49 | .... | 2/26/31 | 75— 2/28/31<br>(Creat., 3.5)<br>30— 3/16 |
| H. DeW. | 60 | July and November, 1931 | 11/26/31 | 110—11/27/31<br>42—11/30<br>38—12/ 4 |
| C. P. | 58 | June, 1931; then too numerous to count after admission | 8/1/31 | 71— 8/ 3/31<br>95— 8/ 7<br>133— 8/10<br>185— 8/11<br>215— 8/14 |
| B. W. | 49 | March, 1930; 3 attacks since last attack, 3/5/32 | 3/6/32 | 41— 3/ 7/32<br>40— 3/ 9<br>142— 3/28 |
| A. M. B. | 65 | November, 1931 to April 24, 1932, 5 attacks | | 60— 4/30/32<br>47— 5/ 3<br>40— 5/10<br>54— 6/10 |
| J. B. | 64 | .... | 3/24/32 | 48— 3/28/32 |
| S. A. | 68 | July, 1930 | | 46— 1/22/31<br>(Creat., 3.2) |
| J. T. | 56 | September, 1931 | 11/23/31 | 42—11/24/32 |
| S. S. | 48 | Early September, 1932 first attack; several since; worst 11/21/32 | | 29—10/18/32<br>45—11/ 5<br>27—11/14 |

2. From this small group of cases it seems as if (*a*) a rising non-protein nitrogen or (*b*) a non-protein nitrogen that remains elevated in the blood plasma is of ill omen.

3. More attention should be paid to blood chemistry studies during coronary occlusion as a prognostic aid.

4. A lowering of the blood pressure and a diminution in urine output will not alone explain the rise in non-protein nitrogen in acute coronary occlusion.

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## SERUM CALCIUM IN NORMAL BOYS.

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Serum calcium studies were made on 511 cases whose ages ranged from 8 to 20 years. It is within this age group that a paucity of information exists in the current literature.

Cantarow,[1] in his monograph on calcium metabolism, regards the normal range for all ages to be from 9.2 to 11 mg. per 100 cc. of blood. Katzenelbogen and Goldsmith,[2] in a more recent review of the literature, place the extreme normal limits for all ages between 8.6 and 12 mg. per cent. A few studies have been made exclusively on children. Mayer[3] found, among children age between 4 and 10 years, the serum calcium to average 11.38 mg. per cent. Greisheimer[4] *et al.* studied 22 boys between the ages of 7 to 17 years and found that their serum calcium ranged from 10 to 13.5 mg. per cent, with an average of 11.6 mg. per cent. Sokolovitch,[5] in 5 normal children, reported their calcium to be between 9.72 and 11.4 mg. per cent.

Our study was made during the last 2 weeks of July and the first 2 weeks of August, 1932. During this period more than 1 quart of milk was given each boy daily. Fresh fruits and vegetables were abundant, and a well-balanced mixed diet was given. The blood was obtained by venoclysis before breakfast in every instance.

The method used to determine the amount of serum calcium present was that of Clark and Collip.[6] Table 1 gives the distribution of cases. The serum calcium findings of our subjects ranged from 7.6 to 12.5 mg. per cent.

TABLE 1.—TOTAL DISTRIBUTION.

| No. of boys. | Calcium, mg., per cent. | Graphic distribution. |
|---|---|---|
| 1 | 7.6 | — |
| 0 | 7.7 | |
| 1 | 7.8 | — |
| 3 | 7.9 | ——— |
| 4 | 8.0 | ——— |
| 2 | 8.1 | ——— |
| 5 | 8.2 | ——— |
| 5 | 8.3 | ——— |
| 4 | 8.4 | ——— |
| 8 | 8.5 | ——— |
| 4 | 8.6 | ——— |
| 8 | 8.7 | ——— |
| 9 | 8.8 | ——— |
| 11 | 8.9 | ——— |
| 15 | 9.0 | ——— |
| 25 | 9.1 | ——— |
| 25 | 9.2 | ——— |
| 26 | 9.3 | ——— |
| 28 | 9.4 | ——— |
| 30 | 9.5 | ——— |
| 30 | 9.6 | ——— |
| 32 | 9.7 | ——— |
| 35 | 9.8 | ——— |
| 27 | 9.9 | ——— |
| 25 | 10.0 | ——— |
| 17 | 10.1 | ——— |
| 21 | 10.2 | ——— |
| 28 | 10.3 | ——— |
| 15 | 10.4 | ——— |
| 20 | 10.5 | ——— |
| 12 | 10.6 | ——— |
| 5 | 10.7 | ——— |
| 5 | 10.8 | ——— |
| 3 | 10.9 | ——— |
| 5 | 11.0 | ——— |
| 2 | 11.1 | ——— |
| 4 | 11.2 | ——— |
| 3 | 11.3 | ——— |
| 4 | 11.4 | ——— |
| 0 | 11.5 | |
| 1 | 11.6 | — |
| 0 | 11.7 | |
| 1 | 11.8 | — |
| 0 | 11.9 | |
| 1 | 12.0 | — |
| 0 | 12.1 | |
| 0 | 12.2 | |
| 0 | 12.3 | |
| 0 | 12.4 | |
| 1 | 12.5 | — |

Disregarding the highest and lowest 5 per cent of our distributions, we find our normal limits are from approximately 8.5 to 10.8 mg.

per cent. Considering 8.6 to 12 mg. per cent as the extreme normal limits it is seen from the table that 33 are below 8.6 mg. and only 1 above 12 mg.

Greisheimer[4] *et al.* found that the serum calcium content definitely decreased with age. Their average for boys at 12 years of

TABLE 2.—DISTRIBUTION ACCORDING TO AGE.

| Calcium, mg., per cent. | Age. 8. | 9. | 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. | 18. | 19. | 20. | Total. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7.6 | .. | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| 7.7 | | | | | | | | | | | | | | |
| 7.8 | .. | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| 7.9 | .. | .. | .. | .. | .. | .. | 1 | 1 | 1 | .. | .. | .. | .. | 3 |
| 8.0 | .. | .. | .. | .. | .. | .. | .. | .. | 3 | 1 | .. | .. | .. | 4 |
| 8.1 | .. | .. | .. | .. | .. | .. | 1 | 1 | .. | 1 | .. | .. | .. | 3 |
| 8.2 | .. | .. | .. | .. | .. | 1 | 1 | 3 | .. | .. | .. | .. | .. | 5 |
| 8.3 | .. | .. | .. | .. | .. | .. | 2 | 2 | 1 | .. | .. | .. | .. | 5 |
| 8.4 | .. | .. | .. | .. | .. | 1 | 1 | .. | 1 | 1 | .. | 1 | .. | 5 |
| 8.5 | .. | .. | .. | 2 | .. | .. | 2 | 1 | 1 | 1 | .. | .. | .. | 7 |
| 8.6 | .. | .. | 1 | 1 | 1 | 1 | .. | .. | .. | .. | .. | .. | .. | 4 |
| 8.7 | .. | .. | 2 | 1 | .. | 1 | 2 | 2 | .. | .. | .. | .. | .. | 8 |
| 8.8 | .. | .. | .. | .. | 1 | 1 | .. | 2 | 3 | 1 | 1 | .. | .. | 9 |
| 8.9 | .. | 1 | .. | 1 | 2 | .. | 1 | 4 | 1 | .. | .. | .. | .. | 10 |
| 9.0 | .. | 1 | 1 | .. | .. | 1 | 5 | 1 | 6 | .. | .. | .. | .. | 15 |
| 9.1 | .. | .. | 1 | .. | 2 | 3 | 3 | 5 | 7 | 3 | .. | .. | .. | 24 |
| 9.2 | .. | .. | .. | 2 | 4 | 5 | 3 | 5 | 4 | 2 | 2 | .. | .. | 27 |
| 9.3 | .. | .. | 1 | .. | 1 | 4 | 2 | 4 | 9 | 4 | .. | .. | .. | 25 |
| 9.4 | .. | .. | 2 | 2 | 3 | 6 | 8 | 4 | 3 | 2 | .. | .. | .. | 30 |
| 9.5 | .. | .. | 1 | .. | 3 | 3 | 2 | 8 | 9 | 3 | .. | .. | .. | 29 |
| 9.6 | .. | .. | .. | 1 | 3 | 3 | 4 | 7 | 9 | 2 | 1 | .. | .. | 30 |
| 9.7 | .. | .. | .. | 1 | 2 | 4 | 6 | 10 | 8 | 3 | .. | .. | .. | 34 |
| 9.8 | .. | .. | .. | .. | .. | 4 | 5 | 11 | 9 | 3 | .. | .. | .. | 32 |
| 9.9 | .. | .. | .. | 2 | 1 | 1 | 6 | 4 | 9 | 4 | .. | .. | .. | 27 |
| 10.0 | .. | .. | .. | 2 | .. | 3 | 4 | 11 | 2 | 1 | .. | 1 | .. | 24 |
| 10.1 | .. | .. | .. | .. | 1 | 5 | 3 | 2 | 1 | 5 | 1 | .. | .. | 18 |
| 10.2 | 1 | .. | .. | .. | .. | 3 | 2 | 9 | 5 | 1 | .. | .. | .. | 21 |
| 10.3 | .. | .. | .. | .. | 2 | 4 | 5 | 7 | 9 | 1 | .. | .. | .. | 28 |
| 10.4 | .. | .. | .. | .. | .. | 3 | .. | 4 | 6 | 1 | 1 | .. | .. | 15 |
| 10.5 | .. | .. | .. | .. | 2 | 3 | 6 | 2 | 7 | .. | .. | .. | .. | 20 |
| 10.6 | .. | .. | .. | 1 | 1 | 2 | 2 | 4 | 2 | .. | .. | .. | .. | 12 |
| 10.7 | .. | .. | .. | .. | .. | .. | 1 | .. | 1 | 2 | .. | 1 | .. | 5 |
| 10.8 | .. | .. | .. | .. | 1 | .. | 1 | 1 | 2 | .. | .. | .. | .. | 5 |
| 10.9 | .. | .. | .. | .. | .. | 1 | .. | .. | 2 | .. | .. | .. | .. | 3 |
| 11.0 | .. | .. | .. | .. | .. | .. | 1 | 3 | 1 | .. | .. | .. | .. | 5 |
| 11.1 | .. | .. | .. | .. | 1 | .. | .. | .. | 1 | .. | .. | .. | .. | 2 |
| 11.2 | .. | .. | .. | .. | .. | 1 | .. | 2 | 1 | .. | .. | .. | .. | 4 |
| 11.3 | .. | .. | .. | .. | .. | .. | .. | 1 | 1 | .. | .. | .. | .. | 2 |
| 11.4 | .. | .. | .. | 1 | 1 | .. | .. | 2 | 1 | .. | .. | .. | .. | 5 |
| 11.5 | | | | | | | | | | | | | | |
| 11.6 | .. | .. | .. | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. | 1 |
| 11.7 | | | | | | | | | | | | | | |
| 11.8 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 1 | 1 |
| 11.9 | | | | | | | | | | | | | | |
| 12.0 | .. | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| 12.1 | | | | | | | | | | | | | | |
| 12.2 | | | | | | | | | | | | | | |
| 12.3 | | | | | | | | | | | | | | |
| 12.4 | | | | | | | | | | | | | | |
| 12.5 | .. | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| Total | 1 | 2 | 9 | 17 | 32 | 66 | 80 | 125 | 126 | 43 | 6 | 3 | 1 | 511 |

TABLE 3.—DISTRIBUTION ACCORDING TO NATIONALITIES.

| Calcium, mg., per cent. | American. | Polish. | Italian. | Negro. | Others. |
|---|---|---|---|---|---|
| 7.6 | .. | .. | 1 | | |
| 7.7 | | | | | |
| 7.8 | .. | .. | .. | .. | 1 |
| 7.9 | .. | 1 | 1 | .. | 1 |
| 8.0 | 2 | 1 | 1 | | |
| 8.1 | .. | .. | 2 | | |
| 8.2 | 2 | 2 | .. | 1 | |
| 8.3 | .. | 2 | 1 | 1 | 1 |
| 8.4 | 1 | .. | 1 | 2 | |
| 8.5 | .. | 2 | 2 | 4 | |
| 8.6 | .. | .. | 1 | 3 | |
| 8.7 | 1 | .. | 2 | 4 | 1 |
| 8.8 | 3 | .. | 1 | 2 | 3 |
| 8.9 | 3 | .. | .. | 4 | 3 |
| 9.0 | 2 | 2 | 3 | 5 | 3 |
| 9.1 | 3 | 3 | 8 | 5 | 6 |
| 9.2 | 5 | 2 | 4. | 12. | 2. |
| 9.3 | 3 | 5. | 6 | 8 | 4 |
| 9.4 | 7. | 3 | 5 | 9 | 5 |
| 9.5 | 9 | 4 | 7 | 6 | 4 |
| 9.6 | 7 | 6 | 8. | 6 | 3 |
| 9.7 | 9. | 5 | 5 | 11. | 4. |
| 9.8 | 5 | 5. | 8 | 8 | 7 |
| 9.9 | 9 | 3 | 2 | 11 | 2 |
| 10.0 | 4 | 7 | 4 | 7 | 2 |
| 10.1 | 6 | 2 | 2 | 6. | 2 |
| 10.2 | 2. | 4. | 5. | 5 | 5. |
| 10.3 | 5 | 4 | 6 | 7 | 6 |
| 10.4 | 5 | .. | 7 | .. | 3 |
| 10.5 | 4 | 3 | 5 | 8 | |
| 10.6 | 4 | 1 | 1 | 5 | 1 |
| 10.7 | 1 | .. | .. | 1 | 3 |
| 10.8 | 1 | 1 | .. | 2 | 1 |
| 10.9 | 1 | 1 | .. | .. | 1 |
| 11.0 | 2 | 2 | 1 | | |
| 11.1 | .. | 1 | .. | .. | 1 |
| 11.2 | .. | 2 | 1 | .. | 1 |
| 11.3 | 1 | 1 | .. | 1 | |
| 11.4 | 1 | 1 | .. | 2 | |
| 11.5 | | | | | |
| 11.6 | .. | .. | .. | .. | 1 |
| 11.7 | | | | | |
| 11.8 | .. | 1 | | | |
| 11.9 | | | | | |
| 12.0 | .. | 1 | | | |
| 12.1 | | | | | |
| 12.2 | | | | | |
| 12.3 | | | | | |
| 12.4 | | | | | |
| 12.5 | .. | 1 | | | |
| Total | 108 | 79 | 101 | 146 | 77 |

Others:

| | | | | | |
|---|---|---|---|---|---|
| Slavish | 6 | Austrian | 4 | Hungarian | 18 |
| Irish | 8 | Jewish | 6 | Ukrainian | 2 |
| German | 9 | Russian | 16 | Lithuanian | 8 |

age was 11.6 mg., while men at 79 years of age was 10 mg. In our study we found the following for each age group:

11 years of age: average, 9.5 mg. per cent; average deviation, ±0.6.
12 years of age: average, 9.6 mg. per cent; average deviation, ±0.4.
13 years of age: average, 9.5 mg. per cent; average deviation, ±0.58.
14 years of age: average, 9.5 mg. per cent; average deviation, ±0.43.
15 years of age: average, 9.7 mg. per cent; average deviation, ±0.57.
16 years of age: average, 9.7 mg. per cent; average deviation, ±0.73.
17 years of age: average, 9.6 mg. per cent; average deviation, ±0.5.

Apparently there is no decrease in serum calcium in these age areas. It may be that the decrease begins at a later period in life. Howland and Marriott, Kramer, Tisdall and Howland, and Anderson as quoted by Cantarow[1] found no essential difference between the serum concentration in children and adults.

Table 2 gives a composite of the calcium findings according to age. With the thought that there may be some differences, influenced by nationality or race, Table 3 was compiled. No influences, by nationalities or races, were discerned as seen by the central tendencies of the various groups shown below.

The average calcium milligram per cent for the 5 racial categories is as follows:

American, 9.7; average deviation, ±0.5.
Polish, 9.8; average deviation, ±0.6.
Italian, 9.5; average deviation, ±0.5.
Negro, 9.6; average deviation, ±0.5.
Others, 9.7; average deviation, ±0.5.

To discover any possible relationships between behavior, mental development and calcium metabolism, certain psychologic data were obtained. These included the general mental level of each boy of the study, a list of those who have spent 2 or more periods in the special discipline cottage and a list of those who were quartered in the special group of unusually unstable and inadequate boys. No relation was found and the details of this part of the study will be published in a separate paper. As these boys were also all in apparently good physical condition, we feel that they may be regarded as normal.

**Conclusions.** The serum calcium findings on 511 normal boys, between the ages of 8 and 20 years, range from 7.6 to 12.5 mg. per cent. Of the total number reported, 33 were found below and 1 above the extreme normal limits of 8.6 and 12 mg. per cent. Disregarding the highest and lowest 5 per cent of our distribution, we find our normal limits are from approximately 8.5 to 10.8 mg. per cent. No progressive decrease was found with age in our group. Nationality and race, in our findings, showed no influence on serum calcium metabolism.

NOTE.—We desire to thank Dr. John Reinhold of the Philadelphia General Hospital for his help in furnishing the standard oxalate solution and in useful suggestions and criticisms.

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## CALCIUM PRECIPITATIONS AND ALKALINIZATION IN AËROBIC TISSUE CULTURES.

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In a recent paper Demuth[1] described the occurrence of dense, grayish white precipitation rings, which appeared dirty brown in transmitted light, surrounding the explant in the tissue culture medium. Demuth believes that their formation depends upon the glycolytic activity of the cells and concludes from his investigations that these rings are mainly composed of calcium lactate and are formed according to the principle active in the production of Liesegang rings. He obtained these rings quite regularly when small amounts of calcium chlorid were added to the medium, and especially in cultures of malignant cells thus treated. But he observed them also occasionally in well-growing cultures of untreated normal tissues, which, as he remarked, do not produce any excessive amounts of lactic acid, indicating that other slightly soluble salts might form or participate in the formation of precipitates in tissue cultures.

During an investigation by the authors of the effects of various amino-acids upon the differentiation and proliferation of cells *in vitro*, similar formations were first observed in a series of Carrel flask cultures which had been explanted in an ordinary chicken plasma-embryo extract medium to which small amounts of arginine had been added. A more thorough study of the nature and causative mechanism of these precipitations seemed to be indicated, as our findings differed in certain respects from those made by Demuth, and as this author's explanations in regard to the causes and composition of these rings did not appear to be quite applicable to the precipitations observed in our cultures.

The precipitations appearing in our cultures were of grayish-white color and were of three different types. In some of the cultures a delicate, veil-like, white opaque membrane was formed which covered the whole surface of the medium and was loosely attached to it. The growth of the explanted cells was apparently not interfered with. In other cultures the clear plasma medium changed around the explant into a milky white material which gradually extended diffusely into the peripheral parts of the medium, leaving only a narrow, clear zone around the explant. The cellular proliferation in cultures with this type of precipitation was in general very scanty or entirely absent, indicating that the physico-chemical changes brought about by the precipitations, or causing them, were unfavorable to growth. The third variety of precipitations observed was similar to the type described by Demuth. While ring formation was seen in some instances in cultures with scanty cell growth, the great majority of the precipitation rings appeared in cultures which showed a good and healthy cell growth (Figs. 1 and 2). It may be mentioned that the above described precipitations were more frequently found in cultures of normal embryonic chicken cells (chondrioblasts, heart fibroblasts) than in cultures of malignant cells (spontaneous mammary carcinoma of white mice, Walker rat sarcoma).

In agreement with Demuth's observations an irregularity in the shape and extent of these rings was sometimes noticed. There were variations in the density and width of the precipitation zone in different sectors of the rings. In other instances, the ring was primarily incomplete and surrounded the explant as a curved sausage-like formation which later on closed—a development which can be reconstructed from the ring in Fig. 1, in which the sector of the ring, secondarily filled in, can easily be recognized because it is less dense. In a few cultures an irregularly shaped precipitation wall, encircling only a part of the proliferation zone, was seen (Fig. 2). There was no appreciable difference between the sharpness of the inner and outer contours of the rings, as was noted by Demuth in his rings. It is also quite evident from the pictures that the rings sometimes interfered definitely with the proliferation and emigration of the cells, especially in cases where they penetrated the rings. There was not infrequently a crowding of cells in the zone inside the ring (Figs. 2 and 3) with evidence of disturbed nutrition of these cells, as manifested by droplet formation and decrease in cell size. Also progressive degeneration of the cells in the inner zone was not uncommon, resulting in complete destruction of these cells, leaving only a small rim of unhealthy looking cells in and beyond the region of the precipitation zone. Further evidence in regard to the damaging effect of the precipitation upon the cells was furnished by the occasional observation of incrustated cells and fibrils in the precipitation zone (Fig. 4).

The precipitations which represent an amorphous whitish material showed in the fixed and stained cultures a high affinity for hematoxylin, suggesting thereby the presence of a calcium compound. The calcium character of the precipitations was definitely established by the incineration method. After incineration of the cultures and removal of the soluble mineral salts by washing the ashed material with distilled water, delicate, concentric lamellæ of calcium oxid and phosphate remained where the precipitation rings had been located. The concentric lamellated arrangement of the calcium ash also furnished, incidentally, supporting evidence for the conception held by Demuth concerning the Liesegang ring nature of this type of precipitation.

In regard to the chemical nature of the calcium compound, Demuth has, as already mentioned, maintained that the rings consist mainly of calcium lactate, as he found that after washing the cultures repeatedly with water for several days (to remove the soluble mineral constituents from the culture) the analysis of the material containing the undissolved rings gave a calcium-lactic acid ratio approximating that present in calcium lactate. It appears doubtful, however, whether from such an analysis these conclusions can justly be drawn, as calcium lactate is moderately soluble in water and one would therefore expect that the washings with distilled water should also have resulted in the solution and removal of the precipitated calcium lactate. Demuth's lactic acid figures obtained in these explants are, moreover, the lowest mentioned in the group of cultures examined, an observation which cannot well be reconciled with his conception, as the binding of the lactic acid by the calcium should result rather in an increased accumulation of lactic acid around the explant, producing high lactic acid figures. Our own findings also do not support his contention. The addition of alcohol to the cultures does not cause a disappearance or diminution of the rings, as it should if the precipitate consisted of calcium lactate, a substance slightly soluble in alcohol, whereas calcium carbonate and calcium phosphate are almost insoluble in this medium. Acetic acid, on the other hand, added to the culture produces a rather rapid disappearance of the precipitates with moderate production of gas, indicating that at least to some extent the precipitates are composed of calcium carbonate. It is, therefore, not justifiable to assume that the precipitates represent mainly and simply calcium lactate, and Demuth's statement that the process of calcium precipitation in tissue cultures is of a complex nature, and that other factors beside the lactic acid formation by the cells contribute to and participate in all probability in their production, appears to be quite proper.

If the conditions present in tissue cultures are studied in regard to the factors which possibly may play a rôle in the precipitation of calcium salts, the following conclusions may be reached. As explants

in Carrel flasks are practically grown under more or less anaërobic conditions (Demuth), favoring the production of lactic acid, especially in malignant cell cultures, and interfering with escape of carbon dioxid, the resulting increase in acid reaction does not facilitate the precipitation of calcium salts. The possibility that the expulsion of carbon dioxid from the medium by the lactic acid may play a rôle in the formation of the precipitates, as suggested by Demuth, cannot be of major importance because of the fact that there will be established an equilibrium of the carbon dioxid content between the gaseous content of the flask and the solid and liquid medium. Moreover, the less soluble calcium salts, such as calcium carbonate and calcium phosphate, will be precipitated before the more soluble ones such as calcium lactate, in case the reaction conditions become unfavorable for the solubility of calcium salts.

That changes in the protein content of the medium surrounding the explants, caused by the utilization of these substances by the cells or their degradation by the proteases present, may play a part in the induction of the calcium precipitations observed, deserves proper attention. According to Wells, Lichtwitz has pointed out "that the precipitation of colloids results in a decrease of the amount of crystalloids which can be held in solution, wherefore the least soluble salts, those of calcium, are precipitated; by laws of osmotic pressure more calcium in solution will then enter to establish equilibrium, be precipitated, and make way for more calcium until the amount of deposit prevents further osmotic diffusion. This should lead to a calcium shell formation in the outermost zone of the affected area, which would limit the deposition." It is obvious that such a mechanism may have contributed in the formation of the calcium rings, but cannot explain the other two types of precipitations described. Supporting such a conception are the findings of Naeslund,[4] who observed the existence of a parallelism between the proteolytic activity of actinomyces and the appearance of calcium precipitations in the medium.

To a certain extent related to the changes in the protein content of the medium is a third factor, namely, the production of substances having a special affinity for calcium salts. The decomposition of nucleoproteins and lecithin may furnish phosphoric acid which has a great tendency to form calcium phosphates. Deuteroalbumoses resulting from protein degradation have, according to Croftan,[5] a high affinity for calcium.

In view of the fact that calcifications occur in those organs which secrete acids and become more alkalin themselves, and considering that an increase in alkalinity of tissue fluids makes calcium salts decidedly less soluble, determinations of pH of the supernatant fluid of our tissue cultures showing calcium precipitations were made and it was found that it was highly alkalin, usually varying between pH 8.2 and pH 9.0. It is evident that this finding may

account, at least to some extent, for the appearance of calcium precipitations in our cultures. But, as it stands in direct contrast to observations of other authors (Demuth,[1] and others), who reported an increasing acidity in tissue cultures, grown in Carrel flasks, an attempt was made to find the cause of this discrepancy.

In these experiments, the common Carrel flasks which were closed by a loosely fitting rubber cap containing a small cotton plug to insure better the sterility of the cultures were used. It appears that our cultures were therefore grown under aërobic conditions, while the cultures of the other investigators, who used tightly fitting caps were kept under more or less anaërobic conditions (Demuth). It could be shown that the aërobicity of the cultural conditions has a definite and constant effect upon the pH of the supernatant fluid, regardless of whether normal or malignant cells were used. The relative anaërobicity is apparently also the reason for the absence of calcium precipitations in cultures grown in sealed depression slides.

The following experiments may best demonstrate the relations existing in this respect.

*Experiment I.*

Chick chondrioblasts, 3 passages old, were explanted in a medium consisting of chicken plasma and embryo extract diluted 1 to 25 with Tyrode solution. Three sets of 8 cultures each were made. In 1 set the reaction of the medium was adjusted with HCl to pH 7.4, in the second set to pH 7.8 and in the third one to pH 8.2. The original pH of the Tyrode solution used was pH 7.9. The following changes in the reaction of the supernatant fluid were observed, when the caps were loosely fitted to the neck of the flasks allowing a rather free access of air:

| Set original pH of medium. | pH of supernatant fluid after 24 hours. | pH of supernatant fluid after 48 hours. |
|---|---|---|
| pH 8.2 set | 9.0 | 9.0 |
| pH 7.8 set | 9.0 | 9.0 |
| pH 7.4 set | 8.9–9.0 | 8.6–8.9 |

*Experiment II.*

| Original pH of medium. | pH of supernatant fluid. | | | |
|---|---|---|---|---|
| | After 24 hrs. | 48 hrs. | 72 hrs. | 96 hrs. |
| 8.1 | 9.0 | 9.0 | 9.0 | 8.9 |
| 7.7 | 9.0 | 9.0 | 9.0 | 8.8 |
| 7.2 | 8.9 | 8.6–8.9 | 8.6–8.7 | 8.4–8.7 |

The flasks of the first 2 sets (pH 8.1 and 7.7) were then sealed by covering the caps and the necks of the flasks with paraffin and the pH dropped on the following day to pH 7.8 and 7.6 respectively. These results demonstrate quite definitely that aërobiosis has an alkalinizing action upon the culture medium, while anaërobiosis has an acidifying effect. It may be mentioned that the cultures were washed every second day with a properly adjusted Tyrode solution and received then an embryo extract dilution of the corresponding pH. The reaction of the supernatant fluid was determined before washing.

Similar results were obtained with cultures of heart fibroblasts. The formation of rings occurred in some instances, while the explanted muscle continued to contract.

In subsequent experiments with malignant tissues the existence of very similar relations between aërobiosis and anaërobiosis respectively and pH of the supernatant fluid was established.

*Experiment III.*

Small pieces of a spontaneous, white mouse mammary carcinoma were explanted in the above mentioned chicken plasma-embryo extract medium and the flasks closed in three different ways. After 24 hours' growth, the pH of the supernatant fluid was determined and the following observations were made, substantiating those reported for normal tissues:

1. Flasks closed as usually with a loosely fitting rubber cap: pH 8.7.
2. Flasks closed with a cotton plug: pH 8.7 to 8.9.
3. Flasks closed with a rubber cap and sealed with paraffin: pH below 7.2.

*Experiment IV.* Walker rat sarcoma.

| Original pH of medium, 8.0. | After 2 days. | 4 days. | 6 days. | 8 days. | 11 days. |
|---|---|---|---|---|---|
| Sealed (pH) . . | 7.9–8.0 | 7.5–7.9 | 7.7–7.8 | 7.7–7.9 | 7.3–7.7 |
| Unsealed (pH) . | 8.8 | 8.4–8.9 | 8.4–8.8 | 7.9–8.3* | 8.7–9.0 |

* During the 6 to 8 day period the flasks were accidentally closed with new, tightly fitting rubber caps, which accounts for the drop in pH present in the supernatant fluid on the 8th day. The use of the old, loosely fitting caps, by which the original aërobic conditions were reëstablished, resulted promptly in a return of the alkalin reaction.

Corresponding to the above described observation on non-sealed flasks, small defects in the sealing of anaërobic cultures manifested themselves readily by their effect upon the pH of the supernatant fluid which did not become more acid, as it ordinarily does, but remained either unchanged or became even more alkalin. This is a highly sensitive reaction. The method of Hastings and Sendroy was used for the determination of the pH of the supernatant fluid in the cultures.

It may finally be mentioned that the addition of arginin or cystein to the medium had no appreciable effect upon the reaction changes observed. It was, however, noticed that precipitations occurred quite frequently in cultures to which arginin had been added. But it appears to be doubtful, if the basic character of this amino-acid has any relation to the causative mechanism.

Through the addition of various indicator dyes (cresol red, bromthymol blue) it was shown that the plasma medium has approximately the same pH as the supernatant fluid, while the explant itself and its proliferation zone appeared to be more acid. The supernatant fluid was removed and the cultures were briefly washed with a phosphate buffer solution of pH 7.0 before the indicator dyes were added to exclude any marked effect of the supernatant fluid upon the result of the test.

The above described findings seem to indicate that the presence of an alkalin reaction (pH 8–9) is one of the essential requirements for the occurrence of calcium precipitations in the medium of tissue cultures. This conception is furthermore strengthened by the observations of Naeslund[4] on bacterial cultures grown under aërobic and anaërobic conditions. This author found that actinomyces

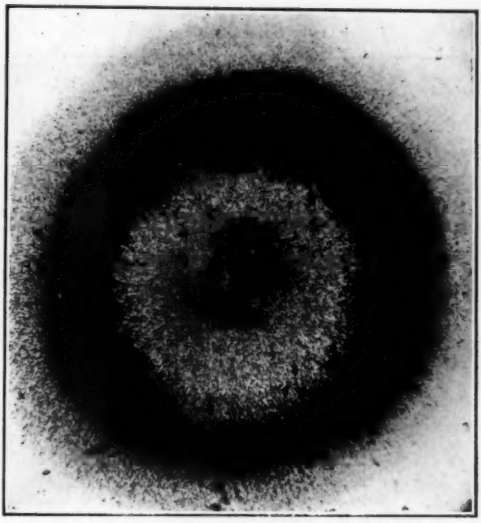

FIG. 1.—A dense and wide calcium precipitation ring which developed in the proliferation zone and which was in the beginning incomplete, becoming closed later, as evidenced by the decreased density of the precipitation in the lower sector of the ring.

FIG. 2.—An irregular precipitation wall encircling only a part of the proliferation zone and showing the crowding of cells behind the wall.

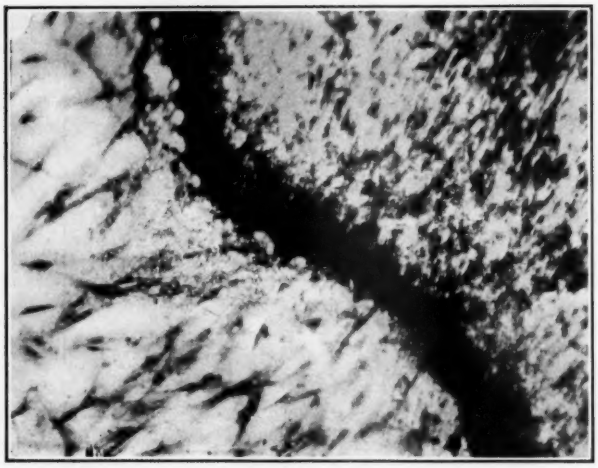

FIG. 3.—High magnification picture of the ring shown in Fig. 2, showing the cells penetrating the precipitation ring, and the difference in morphology and number between the cells located inside of the ring and those outside of the ring.

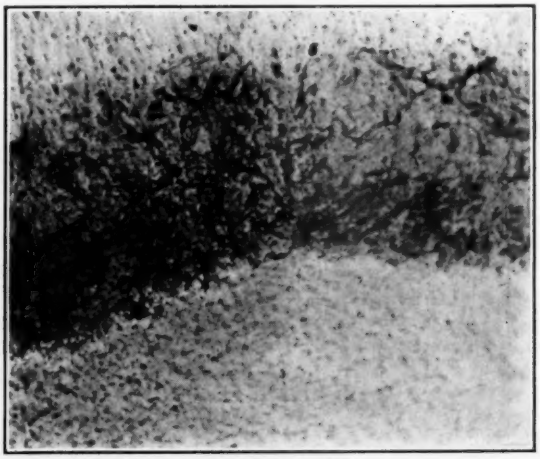

FIG. 4.—A rather weak precipitation ring with calcified cells.

grown under aërobic conditions causes an alkalinization of the culture medium, the pH rising from pH 7.1 to pH 7.5–8.2, with production of marked calcium carbonate precipitations in the medium, while scanty or no precipitations were seen in anaërobically grown cultures, in the presence of a less alkalin pH of the medium. The addition of fermentable sugar on the other hand caused an acidification of the medium and inhibited the production of calcium precipitations. While he considers the change in the pH of the medium the most important factor for the production of calcium precipitations, he believes that the access of carbon dioxid from the air supports their formation, as he observed that filter paper placed on the surface of aërobically grown actinomyces becomes heavily incrustated with calcium salts, obtaining thereby a condition which has a certain similarity to the veil-like membranes covering some of our cultures.

As to the cause or causes of the alkalinization of the medium in aërobically treated cultures, the escape of carbon dioxid from the medium, tending to make it more alkalin, can scarcely account for the large change observed. The formation of rings on the other hand suggests the possibility that the enzymatic activity in the presence of living or dead cells plays a part in the changes of the reaction of the medium and probably also in the physico-chemical constitution and composition of its constituents, both of which may contribute to the production of calcium precipitations as noted above. The question, whether the proteolytic acitivity of the proteases present is involved in this process, cannot be decided with the experimental evidence available. Naeslund suggested the existence of such an interrelation as he found a parallelism between the alkalinization of the medium and the proteolytic activity of the actinomyces. Further investigation would be necessary to determine the chemical character and reaction of the end-products of protein degradation in aërobically and anaërobically grown cultures and their effect upon the pH of the medium, especially in regard to malignant growth, as the conditions present in the aërobic cultures are certainly more comparable to the conditions *in vivo* than those existing in the anaërobic type. It appears certain, however, that the lactic acid generated by the tissues kept under anaërobic conditions prevents the production or counteracts the effect of the basic substances produced. The different types of precipitations strongly suggest, however, that various factors participate in their production and are apparently not the same nor active in all of them.

**Conclusions.** The formation of calcium precipitations in tissue cultures apparently does not depend upon the generation of excessive amounts of lactic acid.

Calcium precipitations have been observed in Carrel flask cultures in which the supernatant fluid had a definitely alkalin reaction (pH 8.2–9.0).

An alkalinization of the supernatant fluid and the plasma medium occurs regularly in cultures of normal and malignant cells grown under aërobic conditions, while an acidification is observed, if the cultures are kept under more or less anaërobic conditions.

The cause or causes for the alkalinization of the medium are not definitely known. The escape of carbon dioxid from the medium can account for only a minor part of the change observed.

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## TYPHOID VACCINE IN THE TREATMENT OF CHOREA.

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The problem of estimating the value of a new method of treatment of chorea is a rather difficult one. Several factors contribute to this difficulty. In the first place, the variability of the natural course of the disease must be kept in mind. It is well known that the ordinary form of chorea tends to spontaneous recovery in from 6 to 10 weeks; exceptionally, it may last 3 or 4 months. Furthermore, not only is there a great variation in the duration of the disease, but also in the severity. Many cases that seem severe at the outset may respond to the ordinary methods of therapy very quickly, while other cases that begin insidiously may be very resistant to treatment. The difficulty in evaluating a new method of therapy is further enhanced by the fact that the patients who are admitted to the hospital may be in the beginning, the middle or at the very end of their attack. It is obvious, therefore, that a therapeutic agent applied in the latter cases would be a very poor criterion as to the efficacy of this agent. In drawing our conclusions we, therefore, took full cognizance of those factors. Anyone who watched our patients with chorea and their response to the treatment could not help being impressed with the prompt and

frequently sudden recovery that followed the introduction of this method of treatment.

It has been repeatedly observed that the course of chorea is sometimes favorably influenced by an intercurrent fever. It is for this reason that non-specific therapy with resulting febrile reactions was introduced into the management of chorea. Horton[1] reported 2 cases of chorea treated by the intravenous injections of a chemically pure protein. This protein was prepared from ox-blood fibrin by peptic and hydrochloric acid digestion. He claimed that his results were good, although the number of cases was very small, and he attributed the favorable effect to the foreign protein only. Mas de Ayala[2] treated a boy, aged 12 years, with chorea by provoking an experimental relapsing fever by the inoculation with Treponema hispanicus. In that particular case all previous treatment such as isolation, rest and the administration of arsenicals had failed. The chorea became progressively worse for a period of 2 years, so that the boy finally was unable to walk. The induced relapsing fever consisted of 4 febrile attacks, and after the second one the patient began to improve. Total and permanent recovery was produced after the 4th febrile attack. Brown, Smith and Phillips[3] reported a series of 23 cases of chorea treated by autoserum injections, intraspinally. Of these, 77 per cent made a complete recovery. Charney[4] reported 2 cases of chorea treated by Small's antistreptococcic serum, with no improvement. Similarly, Williams[5] reported 2 cases treated by the same method with no improvement. Von Kern[6] reported 3 cases of very severe chorea which recovered soon after receiving 3 to 4 intramuscular injections of 5 to 10 cc. of milk at 3- to 4-day intervals. Following the first and second injections, there was some increase in the choreic movements; then a definite subsidence followed the third or fourth injection. Hymanson[7] used boiled milk injections in 7 cases of chorea. Of these cases, 4 showed no reaction to the injection and yet they improved remarkably, showing, he stated, that reactions were not necessarily desirable. The 3 cases, however, that showed the most striking improvement developed a pronounced reaction to the milk injection. Nirvanol or phenyl-ethyl-hydantoin, a more recently introduced therapeutic agent in chorea, certainly acts, not so much because of its sedative effect, but because of the shock or febrile reaction that takes place anywhere from 7 to 12 days after the administration of the drug is begun. Sutton,[8] who first reported the use of typhoid vaccine in the treatment of chorea, states that she came to use it because she wanted to induce a febrile reaction. The desirability of this febrile reaction in the treatment of chorea suggested itself to her when a patient with chorea, who was getting phenolbarbital, improved after developing a barbital reaction associated with fever. She was not the first one, however, to observe the value of the typhoid fever reaction in chorea. Twenty-five

years ago a Roumanian physician, Mor Turnovszky,[9] reported a case of chorea which was cured by an intercurrent attack of typhoid fever. He, however, took no advantage of this observation and did not follow up any further cases.

Our method consisted in injecting intravenously a mixture of typhoid, paratyphoid A and paratyphoid B vaccine, each cubic centimeter containing 500,000,000 of typhoid, 250,000,000 of each paratyphoid A and B organisms. The initial dose was anywhere from 0.15 to 0.2 cc. Very soon afterward the child developed a definite and marked chill, followed by a rise in temperature which reached its peak in about 3 to 4 hours, and was usually down to normal in 6 to 8 and occasionally 10 to 12 hours. Most patients would have a sharp reaction of this type following the initial dose but would not react thereafter unless the dose was increased, and this was usually done in amounts of 0.1 cc. per injection per day. However, when the patient did not react to the initial dose of 0.15 to 0.2 cc., or to an increase of 0.1 cc. per day, then the increase in dosage was made more rapidly. We have had cases, however, that reacted sharply to the same dose daily, that is, to a dose of 0.2 cc., and in those cases no daily increase in dosage was made. In a few patients we noticed a secondary rise in temperature the day after the injection. Where that occurred, we either delayed for 24 hours the next succeeding injection, or we did not increase the dose of the injection on that day and, instead, used the same dose that was used on the previous day. The injections would be continued daily, usually for 6 or 7 days, when a rest period of several days would be instituted. Where the child did not recover completely after the first series of 6 or 7 injections, a second, third or even fourth series of injections would be instituted. A decided benefit from the injections was usually observed very soon after the second or third injection, and frequently there would be a complete disappearance of the choreic symptoms before the first series of 6 or 7 injections was completed. The usual rise in temperature was between 102° and 104° F. Where the reaction was very severe and the rise in temperature a very high one, then the same dose was given the next day, or the increase in dosage was only 0.05 cc. instead of 0.1 cc. We have noticed that the cessation of choreic movements did not occur as rapidly in those patients who did not have a marked febrile reaction following the injection of the vaccine. In cases of this type we resorted to a much larger dose, in 1 patient using as much as 1.5 cc. of the vaccine in the final injection.

No untoward effects were observed from this form of therapy in 23 patients who received a total of 297 injections. There was a slight loss of weight because of the temporarily induced anorexia as a result of the fever, but this was gained back very quickly as soon as the injections were stopped. We could discern neither ill-effects nor beneficial effects from the "typhoid shock" upon an

accompanying endocarditis, of which we had 3 cases. Whenever a rapid pulse existed before the vaccine treatment was undertaken, the tachycardia was still present after the effects of the typhoid reaction subsided. The increased pulse rate which accompanied the high rise in temperature following the vaccine administration was in proportion to the rise in temperature. Hench,[10] who studied the reactions to injections of typhoid vaccine intravenously for other conditions than chorea in about 2500 patients, representing an aggregate of about 10,000 injections, found that the reactions were in general well borne, and that unusual reactions were rare. In his series they occurred in 14 cases, an incidence of about 0.5 per cent of the patients. The unusual reactions that he noted were as follows: acute and subacute appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, extensive vascular thrombosis and renal insufficiency. We noticed absolutely no complications nor deleterious reactions. The recovery from the "shock" was, as a rule, prompt and complete.

We studied 23 patients, 11 boys and 12 girls. The oldest child was 12 and the youngest 4, the average age being $8\frac{1}{2}$ years. We divided them, from the point of view of duration, into acute, subchronic and chronic cases; the acute were those who suffered from the disease up to 2 weeks before therapy was begun; the subchronic, up to 6 months; the chronic, over 6 months. Of these patients, 9 (40 per cent) suffered from chronic chorea, in whom the average duration of the chorea was about $4\frac{1}{2}$ years; 6 patients suffered from subchronic, with an average duration of about 4 months; 8 cases were of the acute type, in which the duration of the disease was on an average 11 days before admission to the hospital. Only 3 of the 23 patients had cardiac complications of the mitral type. It is rather significant that the majority of the patients had a low leukocyte count, and some even a leukopenia, before treatment was begun. This finding was the same in the chronic as well as in the subchronic and acute cases. Of the 23 cases, 11 had a leukocyte count of 8000 or over. The average white blood cell count of the remaining 12 cases was 5800, a definite leukopenia. The average white blood cell count on admission for the total 23 cases of chorea was 7500.

Of the 23 cases, 19 were entirely well at the time of discharge from the hospital. In 1 case of chronic chorea there was only a persistent talkativeness, but all other signs and symptoms were gone. One chronic case showed a persistent blinking, and 1 subchronic case was transferred to another hospital because of an intercurrent infection soon after the course of injections was completed. Only 1 of the 23 cases, a subchronic one, was definitely refractory to treatment, the twitchings and irregular movements persisting in spite of the treatment; however, on follow-up examination, 2 months later, this patient was entirely symptom-free.

TABLE 1.—RÉSUMÉ OF ESSENTIAL FINDINGS IN 23 CASES.

| Case No. | Name. | Sex. | Age, yrs. | Past history. | Chief complaint. | Duration of illness before treatment. | Physical findings. | White blood cell count. | Number of admissions. | Previous treatment and result. | Number of series of injections. | Total number of injections. | Total amount of vaccine received. | Condition on discharge. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | J.C. | M. | 10 | Measles | Twitching | Over 1 yr. | Irregular movements of all extremities; organic systolic murmur in mitral area | 5800 and 3000 Av. 4400 | 3 | Discharged unimproved after 6 wks. in hosp.; 2d admission, rest in bed and various drugs gave no relief; given 3 injections of vaccine, 0.2 cc. each; improvement but still some residual twitchings on discharge | 5 | 20 | Cc. 7.55 | Symptom-free | Steady and continuous improvement after injections were begun. |
| 2 | H.G. | F. | 9 | Measles, tonsillitis; "heart trouble" for past 2 years | Chorea and mitral valve disease | 4 mos. | Could not sit quietly; kept moving head and hands; thin and pale and definite evidence of mitral and early myocard. disease | 9700 | 1 | Not known | 1 | 7 | 1.40 | Symptom-free | After 7th injection only a few irregular movements; chorea disappeared in 1 mo. and did not recur during 6 wks.' observation. |
| 3 | E.T. | F. | 12 | ..... | Constant irreg. movements of extremities and tossing in bed | 1 wk. | Neg. except for chorea and slight sec. anemia | Av. 7500 | 1 | None | 1 | 7 | 1.40 | Symptom-free | Movements subsided after 7 injections; no recurrence during 2 mos.' observation. |
| 4 | R.M. | M. | 10 | ..... | Nervous and twitching; unable to study; wriggling constantly and twitching of mouth and chewing of tongue | 1 yr. | Moderate sec. anemia; heart neg.; typical choreiform movement | Av. 10,600 | 2 | After 8 injections, 0.2 cc. each, restlessness disappeared but least excitement caused jerky movements; 5 more injections, 0.2 cc. each, produced still more improvement but a residual jerking when excited | 3 | 19 | 4.90 | Only slight improvement | Only refractory case in entire series of patients. |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | M. G. | F. | 11 | Measles, tonsillitis; T. and A. 2 yrs. ago | Shaking and dropping of articles; gradually getting worse; loses temper easily and becomes excited very rapidly; last 2 wks. much worse | 3 mos. | Neg. except for choreiform movements | 5300 | 1 | Not known | 1 | 11 | 2.00 | Symptom-free | After 5th injection considerable improvement; chorea stopped after 10th injection. |
| 6 | J. G. | F. | 9 | Measles, chickenpox, whooping cough | Constant restlessness; difficulty in talking; jerky movements; paralysis of left arm and left leg | Definite history not obtainable | Choreic movements; flaccid palsy of left side of face, left arm and left leg; unable to talk or walk; decided sec. anemia | 6900 | 1 | Not known | 2 | 19 | 3.00 | Palsy disappeared and marked improvement in choreic symptoms | Mother had rheumatism and "heart trouble" when young; sister had chorea; observations were stopped by development of contagious disease. |
| 7 | M. S. | M. | 11 | Measles, mumps, pertussis, varicella and scarlet fever, rheumatic fever, tonsillitis | Marked generalized twitching | 4 yrs. | Chorea; functional systolic cardiac murmur; no anemia | 7400 | 2 | After 5 injections, 0.3 cc. each, through 11 days, symptoms subsided entirely; 2 wks. later recurrence of some twitching of face and hands | 2 | 11 | 3.15 | No twitching, persistent occasional blinking of eyes | |
| 8 | G. D. | M. | 11 | Measles, pertussis and varicella | Twitchings of face and arms | 1 yr. (second attack) | Chorea; no cardiac involvement; moderate sec. anemia; stool examination neg. for ova and parasites | 5300 | 1 | First attack 6 yrs. ago; after elimination of seat worms chorea disdisappeared; second attack, unimproved despite varied therapy, including circumcision | 1 | 5 | 1.00 | Symptom-free | Chorea disappeared after 5 injections; observed for 3 wks. without recurrence of symptoms. |
| 9 | J. G. | M. | 10 | Measles, pertussis, mumps, varicella, tonsillitis | Nervousness; shrugging of shoulders; wrinkling of face; spells of irritability | 6 mos. | Neg. aside from choreic symptoms | 5700 | 1 | Watched in ward for a week, without any treatment while movements continued | 1 | 7 | 1.35 | Symptom-free | Twitchings stopped after 9 days of vaccine therapy; no return of symptoms during more than 3 mos. observation. |
| 10 | F. O. | F. | 6 | Measles | Twitching of shoulders; rolling of eyes; inability to write because pen suddenly jerks off paper | 7 mos. | General condition good except for severe chorea | 8000 | 1 | Not known | 2 | 19 | 5.00 | Symptom-free | Mother had chorea; 8 days after admission twitchings improved; movements ceased after 16 days. |
| 11 | J. I. | M. | 7 | Smallpox, measles and rheum. fever; 3 yrs. ago had automobile accident and 3 days after irreg. movements and grimaces developed; tonsils removed but twitchings continued | Very talkative, constant facial grimaces and generalised restlessness off and on; unable to sleep and violent temper | 3 yrs. | Normal heart; no anemia; marked chorea | 6600 | 1 | Not known | 1 | 11 | 2.20 | All symptoms cleared up except talkativeness | Only patient who developed a febrile reaction but no chill following the vaccine injections. |

TABLE 1.—RÉSUMÉ OF ESSENTIAL FINDINGS IN 23 CASES.—*Continued.*

| Case No. | Name. | Sex. | Age, yrs. | Past history. | Chief complaint. | Duration of illness before treatment. | Physical findings. | White blood cell count. | Number of admissions. | Previous treatment and result. | Number of series of injections. | Total number of injections. | Total amount of vaccine received. | Condition on discharge. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | V. N. | F. | 4 | ..... | Twitching, nervous and fidgety, esp. in past week; would not eat and always appeared tired; spilled food because of shaking of hands | 2 wks. | Moderate sec. anemia; marked chorea | 3300 | 1 | None | 4 | 24 | Cc. 10.60 | Symptom-free | |
| 13 | B. C. | F. | 6 | ..... | General twitching with pain about heart; began with slight twitching of left arm, spread to left leg and soon became generalized | 12 days | Mitral disease; choreiform movements | 10,600 | 1 | None | 2 | 12 | 7.30 | Symptom-free | Unchanged after 1st series; rest 2 wks.; choreiform movements, after 2d series completed, stopped sharply. |
| 14 | R. D. | F. | 9 | Diphtheria, measles, mumps, pertussis, bronchopneumonia, frequent sore throat and colds | Jerky movements; drags foot and throws hands around | 6 yrs. | Normal aside from chorea | 10,200 | 1 | Treated repeatedly by medication and rest, without any improvement | 2 | 12 | 3.45 | Symptom-free | No change after 1st series; rest 9 days; 3 days following completion of 2d series chorea stopped; no recurrence during 27 days' observation. |
| 15 | M. L. | M. | 8 | ..... | Choreic movements | 2 yrs. | No cardiac involvement; chorea | ... | 1 | Rest in bed for 3 wks. but no relief from symptoms | 2 | 14 | 4.24 | Symptom-free | Movements disappeared for 12 days; after 2d series disappeared entirely. |
| 16 | J. W. | M. | 11 | First attack of chorea 6 yrs. ago; constantly getting worse | Consid. facial grimaces; difficulty in walking, talking; inability to eat; one of our worst cases | 6 yrs. | Slight sec. anemia; neg. except for severe jerking of extremities, grimaces, inability to talk, eat or walk; quite uncontrollable | 9200 | 1 | For 64 days given complete isolation, salicylates, bromids, luminal, codein and morphin, without any effect on condition | 2 | 16 | 1.94 | Symptom-free | Striking therapeutic gain; 6 days after vaccinotherapy was begun, first definite improvement and a lessening of speech defect; 27 days after, movements subsided entirely, and remained well for 37 days' observation. |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | F. C. | F. | 10 | Varicella, measles and pertussis | Jerking and twitchings | 5 days | Neg. aside from chorea | 9500 | 1 | None | 2 | 29 | 15.40 | Symptom-free | Definite improvement following each "vaccine shock;" at end of 50 days' hospitalization, was discharged cured. |
| 18 | E. W. | M. | 10 | Rheumatic fever, 4 and 3 yrs. before admission; measles | Spasms and twitchings | 17 days | Enlarged tonsils; loud systolic murmur in mitral area | ... | 1 | Treated in usual way, without improvement | 1 | 6 | 1.20 | Symptom-free; murmur disappeared as choreic movements subsided | Within 8 days after 1st injection patient improved and injections were stopped. |
| 19 | H. W. | F. | 11 | Measles, mumps and varicella; T. and A. 5 yrs. before present illness | Nervous and irregular movements steadily worse; unable to sit still | 2 mos. | Neg. except for chorea | 8000 | 1 | Not known | 1 | 12 | 2.40 | Considerable improvement | Within 15 days after injections were begun, considerable improvement noted. |
| 20 | T. W. | M. | 10 | ..... | Spasmodic jerking of muscles, continually growing worse | 13 wks. | Loud systolic murmur in aortic area; severe chorea | 10,800 | 1 | Not known | 1 | 11 | 2.20 | Symptom-free; murmur disappeared as movements subsided | Marked improvement after 6th injection. |
| 21 | D. S. | F. | 10 | Scarlet fever, diphtheria, measles, varicella, pertussis and frequent sore throat colds | Twitchings | 6 yrs. | Neg. except for chorea | 9000 | 1 | Not known | 1 | 9 | 1.80 | Symptom-free | Definite improvement after 5th injection. |
| 22 | L. L. | F. | 9 | Measles, mumps and chickenpox; T. and A at 4 yrs. of age | Continuous twitchings of mouth and facial muscles; considerable and constant irreg. movements of arms and legs | Definite history not obtainable | Neg. except for chorea | 6800 | 1 | Received Small's S.C.A. vac. and sympt. were definitely aggravated; put on bromids, luminal, acetyl salicylic acid, antipyrin, salicylates and kept at absolute rest; these measures continued for 33 days, with no improvement whatsoever | 1 | 8 | 1.60 | Symptom-free | After 3d injection, settled down and rested quietly; 10 days after vaccinotherapy was begun, movements disappeared altogether; was discharged cured after 15 days from beginning of the vaccinotherapy. |
| 23 | S. S. | F. | 8 | Tonsillitis, whooping cough, cervical adenopathy | Twitching; nervousness; restlessness and tossing about of left upper extremity; peculiar speech | 2 wks. | Malnutrition; diseased tonsils; marked cervical adenopathy; soft systolic murmur was heard over entire precordium | 9000 | 1 | None | 1 | 8 | 2.80 | Marked improvement | |

Cases 1 to 15 studied at Jefferson, 16 to 21 at St. Christopher's, 22 at Memorial and 23 at Jewish Hospitals.

The most significant fact to be emphasized in this study is the remarkable effect of this form of therapy on the chronic cases. Of the 9 chronic cases in which the chorea had persisted on an average of $4\frac{1}{2}$ years, 8 became entirely symptom-free and 1 showed only a persistent blinking of the eyes at the time of discharge from the hospital.

There are several criteria by which we may measure the efficacy of a new method of treatment of chorea: (1) The rapidity of the disappearance of the symptoms; (2) whether or not the patients continue to be free from choreic movements after the treatment is stopped; (3) whether or not the new method, in comparison to the older forms of treatment, shortens the hospitalization period; (4) in what percentage of the cases, if any, there is a recurrence of the chorea. We were quite struck by the marked rapidity with which the symptoms of chorea disappeared following the vaccine injections. We were able to continue our observation on the patients for quite a while following the cessation of therapy, because at the time of our study we were not interested in the third criterion, namely, the length of the hospitalization period. Many of the patients were kept in the hospital for a period of 1 and 2 months in order to observe them further and watch for any recurrence of the symptoms. Several of the patients went home and returned later for the removal of tonsils and adenoids, and they were still free from choreiform movements. Two of the cases were readmitted at a later date on account of the cardiac condition, and they also showed no evidence of recurrence of the chorea.

Eleven patients returned for follow-up examination. The findings are summarized in Table 2. As will be discerned, out of the 11 cases, 9 were chronic, 1 subchronic and 1 acute. The patients were reëxamined 3 to 15 months following their discharge from the hospital. Of the 9 chronic cases, 5 were entirely well; the 1 subchronic and 1 acute case were well; of the 4 remaining chronic cases, 1 only showed a certain amount of general restlessness but no actual twitching, and the remaining 3 a recurrence of choreiform movements. Out of 11 cases possibly 7 or 8 were therefore still free from choreiform symptoms upon reëxamination 3 to 15 months later, in spite of the fact that 6 of them were chronic choreic patients and had been suffering from chorea an average duration of over 4 years prior to the time when vaccinotherapy was started.

**Discussion.** The majority of observers that reported favorably on the effectiveness of nirvanol in the treatment of chorea consider that its use is not justifiable on account of the severe and dangerous reactions which may follow, and which are neither predictable nor preventable. Pilcher and Gerstenberger,[11] in reporting on their results with nirvanol, state that the complications usually consist of "irritation of the mucous membranes, stomatitis, conjunctivitis, edema of the face, and urticaria and, rarely, vulvovaginitis, balanitis and irritation of the urinary tract with bloody urine. In 1 case

TABLE 2.—FOLLOW-UP EXAMINATIONS OF 11 CASES OF CHOREA.

| Case No. | Name. | Type of case. | Time elapsed since discharge from hospital. | Condition at present. | Remarks. |
|---|---|---|---|---|---|
| 1 | J. C. | Chronic | 7 mos. | Well | |
| 2 | H. G. | Subchronic | 4 mos. | Well | Marked impr. of heart; mitral disease still present. |
| 4 | R. M. | Subchronic | 3 mos. | Well | Shows complete recovery, though refractory when discharged. |
| 7 | M. S. | Chronic | 14 mos. | Irreg. movements of head and eyes | |
| 8 | G. D. | Chronic | 15 mos. | Well | |
| 9 | J. D. | Chronic | 10 mos. | Well until 6 weeks ago occ. twitching of nose and blinking began | |
| 10 | F. O. | Chronic | 4 mos. | Well | |
| 11 | J. I. | Chronic | 11 mos. | Chr. blepharitis and chr. rhinitis; occ. blinking due to blepharitis | W.B.C., March 9, 1933, 7100. |
| 12 | V. N. | Acute | 9 mos. | Well | W.B.C., August 31, 1932, 3700; January 7, 1933, 8800. |
| 14 | R. D. | Chronic | 6 mos. | Twitching of face; irreg. movements of hands, recurring 1 month ago | |
| 15 | M. L. | Chronic | 3 mos. | Some restlessness but no definite twitchings | |

there was exudation into the lungs, resembling pneumonia." Feer[12] observed a boy with chorea who developed the alarming syndrome of agranulocytic angina following the usual dose of nirvanol for chorea. This boy eventually recovered. In rabbits large doses led to exhaustion of the bone marrow and agranulocytosis. These disturbing symptoms or complications have never been observed in the 23 cases that we hereby report on the use of typhoid vaccine in the treatment of chorea, nor have they been mentioned by Sutton[8] nor reported by Hench[10] in his studies on the reactions to injections of typhoid vaccine for other conditions than chorea. Furthermore, nirvanol seems to be most effective in the first attack or in acute chorea, whereas typhoid vaccine has been found by us to be most valuable, particularly in chronic chorea, that is, those cases that are usually obstinate in character, baffle all therapeutic

attempts, and are resistant to every possible measure ordinarily undertaken for the relief of the condition.

**Summary.** Twenty-three cases of chorea, 9 of which were chronic, were treated by means of typhoid-paratyphoid vaccine, intravenously; 19 were entirely symptom-free at the time of discharge from the hospital. Of the 9 chronic cases in whom the average duration of the symptoms was 4½ years, 1 showed a persistent talkativeness and 1 a persistent blinking of the eyes, but all other symptoms had disappeared. One patient who suffered from chorea for 2 months was improved following the vaccine injections, but we were unable to continue our observations on her because of transfer to another hospital soon after the injections were completed. Only 1 of the 23 patients, a subchronic one, was definitely refractory, and the twitchings and irregular movements persisted in spite of the treatment; nevertheless, when this patient returned 3 months later for follow-up examination he was entirely well. A reëxamination of 11 cases, 3 to 15 months subsequent to discharge, showed 7 and possibly 8 to be entirely well, in spite of the fact that over 50 per cent of them belonged to the class of chronic chorea. No untoward effects were noticed in any of the patients from the vaccine injections. While the number of cases is not very large, nevertheless the uniformity of favorable results points to this procedure as a valuable method in the treatment of chorea, and its effectiveness is especially emphasized in the obstinate and chronic cases.

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## SPONTANEOUS RUPTURE OF THE ESOPHAGUS WITH A REPORT OF FOUR CASES.

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Since the death of Baron Wassenau (1724), attributed by Boerhaave to spontaneous rupture of the esophagus, approximately 40 cases have been reported. It is the purpose of this paper to

submit a brief review of the literature on this subject, to report 4 cases occurring at the Louisville City Hospital and to suggest a few general conclusions regarding this condition.

Fitz[1] (1877), made a complete survey of all the literature on this subject. He concluded that the findings in many of the reported cases were really due to postmortem changes and that in others there was definite evidence of preëxisting disease. He accepted the cases of Allen, Meyer, and Grammatski as being actual spontaneous ruptures occurring in previously healthy esophagi. He explained the rupture, hemoptysis, and subcutaneous emphysema as being a result of straining to expel a foreign body in the esophagus, and attributed the symptom complex and early death to irritation of the vagus and sympathetic nerves, and if prolonged, to gangrene of the mediastinum and lung.

Ziemssen[2] (1878) and MacKenzie[3] (1884) stretched esophagi removed from fresh cadavers with weights, and found that an average of 7 to 8 kilograms was required to rupture the muscularis, while about 10 kilograms were necessary to rupture the mucosa. MacKenzie also produced rupture by exerting 5 to 11 pounds of water pressure within the esophagi.

Brosch[5] (1900), by using water pressure from within—in esophagi removed from fresh cadavers—was able to produce linear rupture of the tubes, always below the point of bifurcation of the trachea, and, in a majority of cases, near and including the cardiac sphincter. In these cases the mucosa was the part first torn. He treated the mucosa of 6 cases with gastric juices at body temperature over periods of 12 to 48 hours. In 4 of these, approximately the same force was required to produce rupture as in the untreated cases. Of the 2 remaining, it is particularly interesting that in 1, a case dying of cerebral abscess in which there was said to have been a contracture of the cardiac sphincter, spontaneous rupture occurred after 35 to 40 hours. Brosch concluded that spontaneous ruptures of the esophagus would occur following emesis, due either to the act (increased intra-esophageal pressure), or secondarily, due to digestion by the gastric juice made possible by the presence of ulceration.

Williams and Boyd (1926), made a linear incision through the lower portion of the esophagus in dogs and then induced vomiting in the animals. Postmortem examination of these animals did not reveal the gross and microscopic changes described in the reported cases and they concluded that spontaneous rupture of the esophagus is preceded by inflammatory changes which weaken the wall.

The following case reports constitute all those recognized at the Louisville City Hospital during the past 10 years, excluding instances of rupture associated with obvious lesions, such as aneurysm or neoplasm.

**Case Reports.** CASE 1.—Female, white, aged 47 years, admitted November 1, 1931. Two hours prior to admission, following what was

described as an average evening meal, the patient became nauseated and vomited. After vomiting she seemed somewhat relieved but after a few minutes vomited again. At this time she suddenly complained of excruciating pain in the lower mid-portion of her chest and cried that she was going to die. She vomited and coughed up a small amount of blood. She was seen promptly by her family physician, who gave her ¼ grain morphin and sent her to the hospital. Previous history was negative except that she had been taking injection treatments for varicose veins for a few weeks prior to admission, having received 4 treatments in all, the last having been about 5 days before. She was said to have been treated several years previously for "heart trouble" but no symptoms could be elicited to support this diagnosis.

Examination revealed a moderately obese white female, aged 47, who was slightly cyanotic, dyspneic, very apprehensive, and obviously critically ill. Her temperature was 97°, pulse 112, respiration 30, and blood pressure 120/70. There was slight subcutaneous emphysema over the lower anterior portion of the neck. Occasional fine inspiratory râles could be heard at both lung bases. There was slight tenderness to deep pressure in the epigastrium. Both legs showed moderate varicosities.

She was kept reasonably comfortable during the next 24 hours with 1½ grains morphin and the use of an oxygen tent. There was slight increase in the subcutaneous emphysema of the neck.

On the 4th day the subcutaneous emphysema—which had involved the face and upper thorax—began to diminish. Findings in the left base were suggestive of beginning bronchopneumonia. The patient was getting nothing by mouth, and glucose and saline were being given intravenously and subcutaneously.

On the 7th day findings in the lower part of the left chest were consistent with fluid, the presence of which was verified by Roentgen ray. About 75 cc. of dark brown fluid with a granular sediment were removed by thoracentesis. This fluid had a very offensive odor, quite similar to the odor of the gas frequently eructated by the patient. She was seen at this time by Dr. August French, Resident in Surgery, who made the diagnosis of ruptured esophagus. The fluid obtained from the thoracic cavity contained free HCl and on culture produced *S. aureus* and *albus*, *B. mucosus capsulatus*, *B. subtilis*, *Lepthothrix buccalis*, and a Gram-negative coccoid bacillus.

On the 10th day a thoracotomy was performed and 2 drainage tubes inserted. There was moderate drainage of brownish fluid—similar to that obtained on thoracentesis—for the next 48 hours and the pleural cavity was irrigated with normal saline.

On the 13th day 150 cc. sterile water containing carmine dye were given by mouth. This appeared in the drainage tubes after about 2 hours.

During the next 4 days the patient became gradually weaker and expired on the 17th day of her illness.

*Autopsy* (Extract). In the lower part of the chest at the left posterior axillary line is a thoracotomy wound in which there are 2 rubber drains.

The left pleural cavity contains air, the lung being collapsed. Both the parietal and visceral pleura are covered by fibrino-purulent exudate. The rubber drains extend well into the dependent part of the cavity. The right pleural cavity contains about 100 cc. of clear, straw-colored fluid.

The esophagus is opened in its lower portion anteriorly and there is found to be a rent measuring 7 cm. in the left lateral portion of its wall opening directly into the pleural cavity. This rent extends from 6 cm. above the cardia through the cardia and dissects the wall of the stomach in pouch-like fashion 2 cm. below the cardia, but does not open into the abdominal cavity.

*Microscopy.* Several sections are taken from the wall of the rent in the esophagus. There is some recent blood clot attached to the surface of the tear. It is lined by granulation tissue, the deepest portion of which is quite well formed. The leukocytic infiltration is moderate, and consists of quite a number of plasma cells and lymphocytes. There are also some endothelial leukocytes and in some areas polymorphonuclears, though these are surprisingly few. The vascular supply of the granulation tissue is abundant and seems consistent with the inflammatory reaction. The epithelium ends abruptly at the edge of the ulcer. Inflammatory reaction extends back under it for a short distance. There is no microscopic evidence of a previously existing ulcer. The arteries and arterioles of the region are for the most part well preserved. Some of them are slightly damaged. Close to the granulation tissue, in fact in the base of it, two vessels are seen which have occluded lumina. These were probably not previously thrombosed; the walls do not indicate a long standing inflammation or sclerosis. It is quite possible that this occlusion has occurred after the rupture of the esophagus. In other words, it does not seem that the organization in the lumen of the vessels is old enough to warrant the interpretation that the wall was weakened by this vessel occlusion and, therefore, ruptured. This organization is recent and very probably the result of the tear, rather than the cause of it.

**Summary of Case.** The patient's death is attributed to the effects of pleurisy, caused by rupture of the esophagus. The shape of the esophageal tear indicates a mechanical factor in its occurrence. The microscopy of this lesion is consistent with the history that it occurred 17 days before death.

Case 2.—Female, colored, aged 52 years. Admitted January 20, 1930. The patient was brought to the hospital in a comatose condition. No reliable history could be obtained. Her son said that she had apparently been in good health up until 3 days prior to admission. At this time she developed a slight "head cold" which became worse. She had a moderate cough, seemed feverish, and was thought to have had one chill. During the 24 hours prior to admission her condition became much worse, she became delirious and hospitalization was advised by a private physician.

Examination revealed a well developed and well nourished colored female, aged 52, who was comatose and obviously moribund. Her temperature was 95°, respiration 60, pulse 180, and blood pressure 60/30.

There was slight drawing of the facial muscles on the left side. The right pupil was smaller than the left; both reacted to light. Her teeth were dirty and carious. There was definite dullness to percussion over the lower third of the chest posteriorly on the left side. Over this area there was a pleural rub. Breath sounds were distant and chiefly bronchovesicular in type. Crepitant râles were present on inspiration. Her extremities were flaccid, tendon reflexes were sluggish, and no abnormal reflexes could be elicited.

The patient did not respond to stimulants and died shortly after arriving in the ward.

*Autopsy* (Extract). The left pleural cavity contains approximately 350 cc. of reddish, slimy, turbid material which looks as though it contained some purulent exudate. There are no adhesions. The tissues of the mediastinum are dark brown in color.

The left lung contains practically no air. Sectioning reveals atelectasis and congestion to a marked degree on left side.

The esophagus is found to have an elliptical opening running longitudinally on its left anterior aspect about 2 cm. in length extending upward from the level of the diaphragm. The remaining gastro-intestinal tract is negative with the exception of a healed ulcer about 2 cm. distal to the pyloric sphincter.

After removal of the skull cap there is a marked flow of spinal fluid.

There is considerable yellow purulent exudate over the base of the brain. This is most marked around the brain stem. The convolutions are slightly flattened.

*Bacteriology.* Smears of the meningeal exudate show a Gram-negative intracellular diplococcus, morphologically a meningococcus.

*Microscopy.* Sections taken from the lesion in the esophagus show a surprisingly small amount of acute inflammatory reaction. This consists only of degeneration and edema. Some of the larger vessels, that is, small arteries larger than arterioles, are moderately damaged by proliferation of the intima. It is estimated that this encroachment on the lumen consists of ¼ to ⅓ of the diameter. Some of the smaller vessels, such as arterioles, are likewise damaged and the encroachment on their lumina is slightly greater; estimated to be ½ in some instances. No vessels are seen which are entirely closed, except for a few in the mucosa. Some of these are possibly entirely closed. The muscle cells are slightly atrophic. There is some hyalin degeneration of the stroma in the submucosa. There is some lymphocytic infiltration about the mucous glands. One lymphatic is seen which is plugged with leukocytes, most of which are polymorphonuclears. Some of the mucous glands are slightly stained with secretion. In 1 of the sections there is a bit of lymphoid tissue. This is probably a normal structure. There is some scarring about some of the mucous glands in the submucosa. This scar tissue is hyalinized.

**Summary of Case.** The cause of death is meningococcic meningitis. The esophagus ruptured a short time before death. The scarring and hyperplasia of the small arteries of the esophagus in the wall of the rent indicate that there was some previous inflammation. The shape of the tear indicates a mechanical factor in its production.

Case 3.—Female, colored, aged 16 years. Admitted April 1, 1930. The patient came to the hospital complaining chiefly of headache. She said that she had been entirely well until 3 to 4 days previously, at which time she developed a head cold. Two days later she developed soreness and stiffness in her back and neck and felt that she was becoming worse. The headache was described as being very severe, constant, and involving the frontal and occipital regions. Her past health was not remarkable.

Examination revealed a well developed and well nourished colored female, aged 16, who appeared very toxic. Her temperature was 102°, pulse 104, and respiration 28.

The head was retracted and the neck rigid. Her skin was moist and hot. The right pupil was widely dilated, the left about normal in size. Neither reacted to light. Examination of the retinæ revealed moderate papillary edema bilaterally. Her tongue and lips were dry and parched. All extremities were spastic, tendon reflexes were hyperactive, and Kernig and Babinski signs were positive.

Spinal puncture revealed a milky fluid under increased pressure which showed ++++ globulin, a 2500 cell count with 95 per cent polymorphonuclears. Primary smear showed Gram-negative intracellular diplococci.

The patient was given antimeningococcic serum into the spinal canal and into the cisterna magna and seemed to improve for the next 3 days. There was some decrease in the muscular spasticity and the patient said she felt much better. During the 3rd night, however, it was noticed that she was having considerable respiratory difficulty and was obviously much worse. Her condition continued critical during the following day and signs were observed in the left lung base which were interpreted as being due to pneumonia. She expired during the night of the 4th day of hospitalization.

*Autopsy* (Extract). The left pleural cavity contains 350 to 500 cc. of dark brown to black fluid, in which particles of food are found. Pressure is made on the stomach and its contents are seen to flow from a rupture in

the lateral border of the esophagus. The opening measures 61 mm. in length and extends upward from the diaphragm. The margins are not discolored and there is no evidence of necrosis. Two small ulcers are seen in the mucosa. The larger one measures 2 mm. in diameter and has a dirty gray friable base. Both parietal and visceral pleura in contact with the fluid are darkly stained. The connective tissue in the mediastinum is hemorrhagic.

The left lung is crepitant throughout. Sectioned surfaces are pinkish-gray and when scraped, reveal deep red firmer areas, giving a mottled appearance. The right lung is normal.

Examination of the brain reveals extensive thick grayish purulent exudate at the base in the subarachnoid spaces.

*Microscopy.* Sections taken from the esophageal lesion show recent necrosis of the connective tissue. This is evidently the result of the action of gastric juice. There is no reaction on the part of the tissue. There is no leukocytic infiltration in the wall of the tear. The vessels are well preserved. There is some extravasation of blood. This blood is partly laked. Some of the vessels near the tear are filled with blood which is partly disintegrated, evidently the result of the action of gastric juice. In one of the sections there is a small amount of leukocytic exudate. This is evidently taken from one of the small ulcers mentioned in the gross description. About these areas there are large masses of bacteria in the tissues. These have a varied morphology, none of them can be definitely recognized as meningococci. Most of them are very large rods.

**Summary of Case.** This patient's condition evidently began as a meningococcic meningitis, which was complicated by a terminal bronchopneumonia and perforation of the esophagus. The esophageal lesion possibly was contributed to by infected emboli. This would account for the small ulcers in the mucosa noted grossly. This interpretation cannot be certain. The histology indicates it is probable. The shape of the tear indicates also that there was a mechanical factor in its production.

CASE 4.—Male, white, aged 60 years. Admitted December 18, 1931. This patient had complained of variable pain in the epigastrium for 2 years. It was said to have been cramping in nature and he was unable to say that food, either in type or quantity, had any definite relation to it. Sometimes he would be symptom-free for several days. At times his discomfort was associated with vomiting, the vomitus said to have consisted of undigested food. The patient had been receiving treatment at the out-patient department during most of this time and a complete work-up was said to have revealed nothing except a questionable duodenal ulcer on Roentgen ray examination. He was referred into the hospital because his improvement had not been satisfactory. His past health was not remarkable. He had used alcohol moderately.

Physical examination revealed a well developed and well nourished white male, aged 60, who appeared in no acute distress. His temperature was 98°, pulse 80, respiration 16 and blood pressure 110/64. His examination was entirely negative except for slight peripheral arteriosclerosis, a senile cataract in the left eye, and slight tenderness to deep pressure in the epigastrium.

A thorough study during 3 weeks revealed nothing except a verification by Roentgen ray of the original impression of duodenal ulcer. All laboratory findings, including gastric analysis, were within normal limits.

There was, however, on 1 Roentgen ray examination, some delay in the emptying of the esophagus which was not present after the use of atropin. Operation was decided upon after a thorough trial with dietary and medicinal measures failed to give the patient satisfactory relief.

On the 25th day of hospitalization under local anesthesia which was later

reinforced by nitrous oxid and a small amount of ether, the duodenal ulcer was excised and a posterior gastro-enterostomy was performed. Considerable adhesions were encountered and the operation required over 3 hours but the patient left the operating room in good condition. The day following operation, his condition became worse. He was slightly cyanotic and vomited about 100 cc. of brownish material. A Levine tube was passed into the stomach and the stomach washed out with tap water. The tube was left in the stomach for constant drainage. His condition continued to become worse during the next day and signs in both lungs were thought indicative of bronchopneumonia. He died at the end of the second day postoperative.

*Autopsy* (Extract). In the midline of the abdomen there is a recent surgical incision. There is a gastro-enterostomy connecting the pyloric portion of the stomach with the jejunum about 5 cm. from jejunal junction. It is well open.

There are old adhesions binding the lung to the parietal pleura on both sides. On the left side there is brownish, straw-colored fluid approximately 250 cc. in amount. On the left side there is mediastinal emphysema. Examination of the mediastinal tissues reveals dark brownish fluid surrounding the esophagus just above the cardiac sphincter of the stomach. The stomach and esophagus are opened by an anterior longitudinal incision and rupture of 2 esophageal ulcers demonstrated. The bases of the ulcers are thin and dark brown in color. They are about 1 cm. in diameter and lie just above the cardia, one on the right and one on the left side. The stomach contains fluid similar to that found in the mediastinal tissues.

In the right lung there is marked congestion and some consolidation of the middle and lower lobes. There is a small amount of thin fibrinous exudate on the surface of the lower lobe. The left lung is similar in appearance, except for a part of lung adjacent to the brownish area in the mediastinum, which appears to be necrotic.

*Microscopy*. Sections of the esophageal perforations show them to be lined with necrotic tissue. There is no repair. There is some proliferation of the intima of the small vessels, especially arterioles.

**Summary of Case.** The patient's death is attributed to bronchopneumonia. The perforation of the 2 esophageal ulcers occurred a short time before death and was undoubtedly a contributing factor. The causes of the ulcers and of the perforations are not demonstrated.

**Comment on Case Reports.** Case 1 represents, as well as may be determined, spontaneous rupture of a previously normal esophagus.

Cases 2 and 3 represent rupture associated with intracranial lesions. The relative frequency of this occurrence has been commented upon by previous writers. Although a definite history of vomiting is lacking in these 2 cases, its occurrence is assumed since the nature of the tears indicate increased intra-esophageal pressure of considerable degree.

In Cases 2 and 4, the arterial changes may have been factors predisposing to rupture.

Case 4 shows evidence of preëxisting abnormality of the esophagus as evidenced by delayed emptying on Roentgen ray examination. Also, there was a mechanical agent in this case which may have produced ulceration. It is unlikely that the tube could have caused the perforations because of the soft texture of the tube used and the ease with which the stomach was entered and the lavage performed.

**General Discussion.** It is generally agreed that the exciting cause of spontaneous esophageal rupture is the increased intra-esophageal pressure incident to vomiting. It is questionable whether or not perforation ever occurs simply as a result of ulceration and digestion by gastric juice. As immediate predisposing causes to rupture—spasm, atony due to repeated vomiting, and digestion by gastric juice are undoubtedly all factors and vary with the individual case. Obstruction of the upper part of the tube by spasm, a foreign body (as food), or from any cause, would obviously make rupture more apt to occur.

While there is some controversy as to the rôle played by pre-existing disease in this condition, it is reasonable to assume that anything which would weaken, or interfere with the normal elasticity or motility of the tube, would make it more liable to rupture. It would follow then, that stricture, vascular thrombosis, infarction, cardiospasm, ulceration, esophagitis, and scar formation predispose to rupture. They have probably been factors in some instances of rupture in so-called normal esophagi.

When one considers the exciting and immediate predisposing causes of esophageal rupture, it is not difficult to understand why it occasionally occurs as a complication of other diseases. In those associated with intracranial lesions, in particular, the frequent tendency to violent vomiting and to muscular spasm makes conditions ideal for such an accident. In fact, it seems surprising that it does not occur—or, at least, is not recognized—more often.

While the exact etiology and mechanism of esophageal rupture are not always apparent, the diagnosis of its occurrence should not be difficult. The sudden occurrence of severe excruciating pain in the lower portion of the chest coming on during the act of vomiting and associated with hematemesis, subcutaneous emphysema of the neck, respiratory distress, and marked prostration, justifies a diagnosis of esophageal rupture. This symptom complex was well illustrated in Case 1 and is so consistently present in the reported cases that it may be regarded pathognomonic of ruptured esophagus.

The subcutaneous emphysema is explained by most writers as being caused by air forced into the mediastinum along with the gastric contents. The explanation of the marked prostration and usually rapid death is, as yet, in dispute. The theory of Williams,[9] 1926, that "death is due to a sudden attack by virulent organisms within an undefended, closed, and toxin-absorptive cavity," seems hardly justified. The organisms thus introduced are mostly non-pathogenic and certainly are of relatively low virulence. Also, the symptoms as observed in Case 1 and as described in the reported cases, are not those of bacterial toxicity, but rather those which would be expected from sudden severe injury to vital structures. It would seem more logical to explain the events by injury to important nerve structures in the mediastinum by the irritation and the

digestive action of the gastric contents as suggested by Fitz[1] and MacKenzie.[3] Such an explanation is supported by pathologic findings and accepted physiology. Bacteria are undoubtedly a factor, probably of increasing importance the longer the patient lives.

Unfortunately, the treatment of these cases offers very little encouragement and the prognosis is extremely poor. The forces which produce the rupture expel a quantity of gastric contents into the mediastinum so that the greatest damage has been done and the outcome usually determined before the patient is seen by the physician. Withholding everything by mouth is imperative as was proved by the administration of carmine dye in Case 1. Sedatives, fluids and nutriment subcutaneously and by venoclysis, and oxygen if there is improper oxygenation of the blood, constitute the other major therapeutic measures. Passage of a tube into the stomach might seem indicated, but the dangers incident to such a procedure —such as the chance of increasing the trauma at the site of the lesion—more than offset its indications. The patient's general condition, certainly in Case 1, and apparently in all reported cases, prohibits surgical procedures directed toward repair of the tear or drainage at the site of the rupture. Immediate surgical drainage of the pleural cavity, as suggested by Boyd and Williams,[9] and urged by Smead,[10] in cases showing rupture into this cavity is not always advisable. In addition to the fact that the patient is a poor risk even for minor surgery, it is not improbable that a great deal of the fluid present in the cavity is produced as a protective exudate and at least early in the condition is actually helpful. It would be better to let the choice of this procedure be determined on the merits of the individual case—being influenced by the patient's general condition and the character of the fluid obtained on thoracentesis. It is significant that there are authentic cases[12] of esophageal rupture with evidence of pleuritis and effusion which have recovered without surgical interference.

**Summary and Conclusions.** 1. The literature on spontaneous rupture of the esophagus is presented and 4 observed cases are reported.

2. The following conclusions are made regarding this condition:

(*a*) Esophagitis, stricture, ulceration, cardiospasm, and vascular changes predispose to esophageal rupture. It may occur, however, in normal esophagi.

(*b*) A sudden onset of pain in the lower portion of the chest, coming on during vomiting, and associated with hematemesis, subcutaneous emphysema of the neck, respiratory distress and prostration, is pathognomonic of esophageal rupture.

(*c*) The symptom complex and usually early death are due to the irritating and digestive action of the gastric contents on the mediastinal structures and pleura.

(*d*) Sedatives, withholding everything by mouth, and the administration of fluids and nutriment by venoclysis, proctoclysis, and hypodermoclysis constitute the more important means of treatment. Oxygen is usually indicated. In the cases presenting evidence of pleuritis and effusion, surgical drainage is indicated in selected cases.

(*e*) The prognosis is always extremely grave.

NOTE.—The descriptions and interpretations of the autopsy findings in the 4 case reports were prepared by Dr. A. J. Miller, Professor of Pathology, University of Louisville School of Medicine.

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## AMEBIASIS IN NORTHERN NEW JERSEY.*

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BROWN,[1] summarizing the cases of amebiasis diagnosed at the Mayo Clinic in the 10-year period, 1921–1931, reported 4 cases from New Jersey. These cases constituting 0.29 per cent of the patients seen from this state, indicate a higher percentage incidence than in many of our Southern states, where endamebal infestation is recognized as flourishing. As search fails to reveal any other cases reported from New Jersey, one would be lead to suspect that amebic dysentery is rarely seen here. To call to mind the endemic nature of this disease, its aspect from the point of view of public health and preventative medicine, and of reporting 5 cases seen in private practice within the past year, we present this paper.

That amebiasis exists in endemic and epidemic form in cities in the northern United States is generally recognized. Kaplan *et al.*[2] report an epidemic in a large hotel in Chicago traced to a kitchen employee who harbored the cysts. Lear and Merrill,[3] in 1924, reported an epidemic in a suburb of New Haven, Conn. Stiles[4] in

* Read before the Academy of Medicine of Northern New Jersey, May, 1933.

1932 stated that of 196 immigrants at Ellis Island 8.6 per cent were infested, and of 2584 American soldiers who did not go to Europe 3.5 per cent were affected. He concluded that the presence of cysts in apparently healthy carriers was common. As early as 1909 Patterson[5] told of 3 cases of amebic dysentery who had never been outside the New York metropolitan area and again called to notice the cases reported by Musser and Stengel in Philadelphia in 1890 and Stockton in New York in 1894. Brooke and Goodale,[6] in 1931, reported 5 cases in Massachusetts. Two of these patients had never been out of the temperate zone. In 1916 Sanford[7] wrote that from 1911 to 1916 that of amebic dysentery at the Mayo Clinic 535 cases had been seen from Northern states and 600 cases from Southern states and the Tropics. None of these cases were Jerseyites but 4 came from New York and 4 from Pennsylvania.

Thus with cases occurring within distance of a Sunday auto ride, in Pennsylvania, New York, Massachusetts, and Connecticut, there is every reason to assume that many cases must exist among us, and we know from personal communications that others have seen these cases though they were not reported.

Craig[8] believes that 10 per cent is the average incidence of infestation in the United States. He finds that 50 per cent of the carriers complain from time to time of gastro-intestinal symptoms, occasional diarrhea, colicky pain, anorexia, flatulence and, at times, tenderness over the liver, leading to a diagnosis of cholecystitis.

The reported incidence of infested carriers varies greatly. Andrews and Paulson[9] state that in 502 unselected people, living at home in Baltimore, 10.9 per cent harbored protozoa in the gastro-intestinal tract, of which only 0.2 per cent had cysts of *E. histolytica*, while Kofoid[10] found 10.8 per cent of troops returning from France infested with *E. histolytica*. It was he who estimated that a healthy carrier passed on the average 14 million cysts per day. In our examination of stools we have been able to demonstrate cysts only in patients suffering from dysentery and have seen no healthy carriers.

**Case Abstracts.** CASE 1.—E. A. E. (referred by Dr. R. W. Tilton), a 40-year-old insurance employee, was a resident of Maplewood, N. J. He suffered from an attack of diarrhea when a soldier in France in 1918 from which, after several weeks of illness, he recovered. He was well until the end of October, 1931 an interval of 13 years. He was seen by us in December 1931 after 6 weeks of continual diarrhea. Physical examination was negative. The liquid stool showed an occasional red blood cell, but no ova. A proctoscopic scraping from the rectal mucosa, examined on a warm slide immediately on removal from the rectum, revealed *E. histolytica* in large numbers. Cure was effected with emetin hypodermically. A check-up on the stools after 1 month revealed no parasites or cysts. This is a case which harbored the parasite for 13 years without apparent symptoms and is similar to the patient reported by Shilling in which he brought up the question of war compensation.

CASE 2.—F. C. B. (referred by Dr. Ripley), a 28-year-old resident of Hackensack, N. J., noted abdominal pain and a looseness of bowel while boating in Florida in 1930. From that time until he was seen by us in 1932 he complained of crampy pains following bowel movements and of

diarrhea. An appendectomy had been performed but afforded no relief. Our proctoscopic examination revealed a slightly congested mucous membrane. His urine contained a trace of albumin and rare granular casts—evidence of a toxic process. His feces were liquid and positive for blood and pus cells. *E. histolytica* were present. He was put on a low residue, high-protein diet and a course of emetin hydrochlorid was instituted. The patient was symptomless by the 7th injection and failed to return for completion of the course.

CASE 3.—C. F. J., aged 40, had a diarrhea of 2 years' duration with blood and mucus appearing daily in his stools. He had had an appendectomy without relief. He was losing weight and seemed to be growing progressively worse. The proctoscope disclosed an ulcerated mucosa, scrapings from which contained what appeared to be dead amebæ. Their morphology was not sufficiently clear to warrant a diagnosis. The stool was liquid and contained blood and pus. No cysts were found. Hopefully 2 series of emetin hydrochlorid were administered at an interval of 2 weeks. This was supplemented by a low residue high-caloric diet. The patient felt better but the diarrhea continued. A second stool left us no better informed than the first examination, but a third stool examination, after several weeks, disclosed numberless cysts of *E. histolytica*. The patient was treated at home. He was given a low-residue diet. Within 10 days the cysts disappeared from his stools and his bowel movements were reduced from 8 to 3 per day. Roentgen examination showed a tubular descending colon and sigmoid, so there is little hope of permanent cure in this case. We feel our patient will suffer from a chronic colitis for the rest of his life.

CASE 4.—C. D. F., a bookkeeper, aged 35, was first seen by us in 1931 when he complained of diarrhea of 5 years' duration. He had 6 to 8 bowel movements a day. An examination of the stool at that time showed the presence of blood. It was otherwise negative. A gastro-intestinal Roentgen ray series was also negative. A diagnosis of colitis was made and the patient was put on a low residue diet and given kaolin (2 gm. t. i. d.) He was relieved and did not return until January, 1933. His symptoms were the same as when first seen. Then proctoscopy revealed typical pin-head ulceration and a proctoscopic smear from the rectal mucosa examined with the warm stage showed many *E. histolytica*. Except for a trip to New England in 1910 the patient had never been outside our metropolitan area but preceding the onset of the present disease he had been engaged in the retailing of vegetables. At that time (1925) he was in the habit of eating raw vegetables from his stand. Particularly was he tempted by Bermuda onions and ate many of them, always uncooked. It is probable that this southern delicacy was the source of his infestation.

It is this case which gives us the most important clue as to the probable epidemiology of amebiasis in this vicinity. The present fad of eating raw vegetables and the increasing quantities of these products being shipped from the South should account for an increase in amebiasis in the next decade.

CASE 5.—C. K., aged 50, an importer of furs, was operated upon by one of us (M. A.) for hemorrhoids, in 1910. The patient had a slight bloody diarrhea after healing of the hemorrhoidectomy wound and, as this continued, Dr. E. J. Ill suggested amebic dysentery. The patient was more or less lost track of until he was again seen in January, 1933. Since 1910 he had had 2 attacks of bloody diarrhea each lasting about 4 weeks. The present 4th attack was of 5 weeks' duration and was accompanied by a perianal abscess. A proctoscopic smear from the rectal mucous membrane was negative, but the stool swarmed with cysts of *E. histolytica*. The source of this patient's infestation no doubt dates back to the Ukraine from which he emigrated to the United States. He said he was accustomed as a child in his fatherland to pick the vegetables from the vines and ground and eat them raw. As he remembered, his father and many of the neighboring farmers suffered from a similar diarrhea.

The symptoms of amebic dysentery are diarrhea and weakness. There is not much pain although there may be occasional colic. The stools are usually liquid, fecal in character and contain blood. The blood may be occult. A proper examination of the stools will show amebæ either in the vegetative or encysted form. With the proctoscope the appearance of the rectum is characteristic. The mucous membrane is studded with small individual ulcers, separated by almost normal or but slightly congested areas.

Noticeable in these cases is that they may continue for years and there may be periods of remission; without treatment the recurrences are apt to be more severe, the bowel becomes more and more involved and some intercurrent infection ends the scene.

The diagnosis is easy if living amebæ are found in the feces or in the material removed proctoscopically from the ulcers. The specimen should be examined as fresh as possible within a few hours after passage, preferable in a warm chamber in order to find living forms. If kept warm for some hours it may be overgrown by colon bacilli. In the cases of chronic diarrhea in which the living amebæ commonly are not found in the stool, a diagnosis is most difficult and several examinations must be made at intervals.

Once the diagnosis is made, the majority of patients are promptly cured by 9 or more intramuscular injections of emetin hydrochlorid (½ to 1 grain). In the long-standing cases with atrophic changes in the bowel wall and stools showing much pus and other evidence of secondary infection, emetin hydrochlorid is not so effective. Manson-Bahr[11] recommends emetin bismuth iodid in these cases in doses of 3 grains per day for 10 or 12 consecutive days. In association with the emetin bismuth iodid, he gives each morning an enema of 2.5 per cent Yatren (iodin-oxyquinolin-sulphonic acid) in warm water (250 cc.). We have used this method in Case 3 with disappearance of cysts from the stool. It was not so successful in Case 5. In association with the treatment we have prescribed the high-caloric, low-residue diet as devised by Bargen and Victor[12] in the treatment of chronic colitis. We have felt that placing the large bowel at rest aids in the healing of the lesions. In the treatment of carriers Craig[13] also mentions the use of emetin bismuth iodid and Yatren. These drugs require that the patient be kept in bed. He found acetarson (Stovarsol) in tablets of 0.25 gm. 3 times a day for 1 week and repeated for a second week after a weeks' rest was effective in banishing the cysts.

Amebiasis is an infestation of the large bowel with *E. histolytica*. Rear Admiral Stitt[14] of our Navy and Manson-Bahr[11] both agree that it is a tropical or subtropical disease. And yet we have found these cases in northern New Jersey in individuals who have never been out of the immediate neighborhood in their lives.

To reconcile these opinions and the findings was a problem but we believe we have found the answer. Although the victims of this disorder did not go to the tropics, the tropics came to them.

The infestation is by the mouth and the tropical and subtropical regions, raw fruits and vegetables are the source of the infestation. Sewage and human excrement have long been used as fertilizer and, though forbidden in our own region, there is no doubt of their use elsewhere.

**Summary.** 1. The endemicity of amebiasis in the states surrounding New Jersey is emphasized.

2. Five cases in New Jersey are reported and the importance of stool examination is stressed as the main factor in diagnosis.

3. Emetin bismuth iodid, emetin, and Yatren are the therapeutic factors of importance.

4. Fresh vegetables from the South are imported to New Jersey throughout the year. Many cases of amebic dysentery in the temperate zone result from eating uncooked contaminated vegetables.

5. A public health warning is uttered to prevent an increase in the cases of this disease.

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## ARACHNIDISM: REPORT OF A SERIES OF 29 CASES OF POISONING FROM THE BITE OF THE LATRODECTUS MACTANS.

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The foreword of one of Emil Bogen's[1] classical papers on arachnidism contains the typical story of a person being most commonly bitten by *Latrodectus mactans*: a young man goes to an outdoor toilet early in the morning, with the resulting inconsequential sting

which he receives on the genitals, followed an hour or more later by the beginning of the dramatic symptoms which mark the climax of poisoning from this insect.

It is a story with which—thanks to the work of Bogen—we are now all more or less familiar; but Bogen[2,3,4] also calls attention to the fact that we have every reason to believe that *Latrodectus mactans* is not only found in outdoor toilets, but invades habitations, entering beds where human beings sleep, and infests houses, garages, automobiles and other places where its presence becomes a menace. He has reported 380 cases with 17 deaths in 18 states.

In the analysis of the 29 cases which we have collected at this hospital, it will be noted that the majority—16 at least and probably more—received their bites while using an outdoor toilet; but it is the minority in which the bites were not received under these circumstances which particularly attracted our attention. These we desire to discuss in some detail. We cannot help but feel that the idea is being spread and believed at the present time that *Latrodectus mactans* bites are necessarily associated with, first, bites received upon the genitals; and second, with the idea that this accident occurs only where people habitually use outdoor privies. The number of cases seen by us which have been bitten under other circumstances reminds us of the fact that this is not invariably true.

The error which we would be most likely to make—and it has been made—is to treat the case as a surgical emergency. The history, in all probability, has played an important part in leading to this unfortunate conclusion. The following case is presented in detail to call our attention to the fact that in these cases the history, as given by the patient—or any statement given by the patient—may be regarded as misleading or valueless.

**Case History.** CASE 1 (56390).—A white male, aged 51 years, presented a very interesting problem when first seen by us.

While working in a field, he was stung between the toes, through the interstices of a broken shoe, by a *Latrodectus mactans*. The symptoms came on rather suddenly, and he was seen by a physician before he was sent to the hospital, who gave him ¼ gr. of morphin, with very little, if any, effect on the pain from which the man was suffering. It was fortunate we saw this man after an experience extending over several years, which left our minds open to the belief that tremendous terrifying symptoms could be produced by the bite of an insignificant-looking insect. Also some of the staff had heard the history from some members of the family over the telephone. To make this matter absolutely certain, some hours later the *Latrodectus mactans* which had bitten the man was brought to us at the hospital. His suffering was so intense that it was the only thing that could engage his consciousness. Later on we were to find out that he did not remember having been brought to the hospital at all, and only returned to a knowledge of his surroundings when his wife came to visit him at about 7 that evening. He had no knowledge of having engaged in conversation with anybody, and the impression we obtained from him when he first came in was that he would have willingly consented to any procedure, surgical or otherwise, if we would only have given him sufficient morphin

TABLE 1.—DESCRIPTION OF FINDINGS IN 29 CASES OF POISONING FROM THE BITE OF LATRODECTUS MACTANS.

| | Case. | Sex. | Color. | Age. | Date. | Temp., °F. | Pulse rate. | Blood pressure. | White blood cells. | Urine. | Urine retention. | Location of bite. | Duration. | Locality. | Abdominal rigidity. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 21011 | M | Wh. | 38 | 7- 9-24 | 97.5 | 80 | ? | ? | ? | No | Penis | 24 hrs. | ? | None |
| 2 | 21591 | M | Col. | 20 | 8- 9-24 | 97.0 | 80 | ? | ? | Neg. | No | Genitals | 48 hrs. | Privy | None |
| 3 | 54133 | M | Col. | 40 | 6-12-29 | 98.0 | 80 | ? | 8,000 | Neg. | No | Scrotum | 3 days | Privy | Intense |
| 4 | 47810 | M | Col. | 53 | 7- 8-28 | 98.0 | 100 | 155/115 | 9,000 | Alb. 3 plus | No | Scrotum | 3 days | Privy | Moderate |
| 5 | 35832 | M | Wh. | 24 | 9-22-26 | 98.6 | 80 | ? | ? | ? | Yes | Penis | 2 days | Privy | Moderate |
| 6 | 35843 | M | Col. | 23 | 8-23-26 | 98.0 | 90 | ? | 16,000 | Alb. 1 plus | No | Penis | 4 days | Privy | Intense |
| 7 | 34754 | M | Col. | 44 | 8- 5-26 | 99.0 | 95 | ? | 8,250 | Occ. r.b.c. | No | Penis | 24 hrs. | Privy | Moderate? |
| 8 | 28776 | F | Wh. | 8 | 9- 7-25 | 98.0 | ? | ? | 19,000 | ? | No | Hip | 24 hrs. | ? | Intense |
| 9 | 59682 | M | Col. | 23 | 4- 4-30 | 99.8 | 85 | 150/100 | 6,000 | Neg. | No | Penis | 3 days | Privy | Intense |
| 10 | 56390 | M | Wh. | 51 | 9-30-29 | 99.0 | 52 | 138/84 | 10,000 | Neg. | No | Foot | 2 days | Field | Very intense |
| 11 | 56751 | M | Wh. | 16 | 10-19-29 | 98.0 | 80 | 140/72 | 15,000 | Neg. | No | Finger | 3 days | Garage | Intense |
| 12 | 13309 | M | Wh. | 19 | 10-30-29 | 98.0 | 72 | 112/70 | ? | ? | No | Hand | ? | Car | Moderate |
| 13 | 63505 | F | Wh. | 50 | 10-17-30 | 98.6 | 98 | ? | 11,000 | Neg. | No | Vulva | 3 days | In bed | Moderate |
| 14 | 67219 | M | Col. | 26 | 5-31-31 | 98.6 | 85 | 150/90 | 9,000 | Neg. | No | Penis | 2 days | Privy | Very intense |
| 15 | 68374 | M | Col. | 31 | 8- 3-31 | 98.8 | 48 | 145/110 | 9,000 | Neg. | No | Scrotum | 2 days | Privy | Intense |
| 16 | 69339 | M | Wh. | 45 | 10- 1-31 | 98.0 | 80 | 138/80 | 12,000 | Neg. | Yes | Penis | 24 hrs. | Privy | Intense |
| 17 | 69673 | M | Col. | 16 | 10-24-31 | 99.6 | 95 | ? | 10,500 | Neg. | No | Genitals | 24 hrs. | Bowling alley | Moderate |
| 18 | 70047 | F | Wh. | 46 | 11-17-31 | 99.5 | 80 | ? | 6,500 | Neg. | No | Leg | 12 hrs. | Kitchen | Moderate |
| 19 | 70078 | M | Col. | 34 | 11-20-31 | 98.0 | 66 | 150/80 | 9,750 | Neg. | No | Penis | 3 days | Privy | Intense |
| 20 | 70168 | M | Wh. | 30 | 11-28-31 | 98.0 | 85 | 138/90 | 15,000 | ? | No | Genitals | 24 hrs. | In bed | Intense |
| 21 | 70805 | M | Col. | 38 | 1-15-32 | 97.0 | 44 | 135/100 | 7,000 | Neg. | No | Genitals | 2 days | Privy | Moderate |
| 22 | 71071 | F | Wh. | 30 | 2- 3-32 | 98.4 | 80 | 130/90 | 26,000 | Neg. | Yes | Genitals | 3 days | Privy | Moderate |
| 23 | 71910 | F | Wh. | 27 | 4- 4-32 | 98.8 | 90 | 146/110 | 9,500 | Alb. 2 plus | No | Leg | 24 hrs. | ? | Intense |
| 24 | 72276 | M | Col. | 28 | 4-30-32 | 97.7 | 80 | 184/116 | 7,000 | Alb. 2 plus | No | Penis | 48 hrs. | Privy | Moderate |
| 25 | 73320 | M | Col. | 51 | 7-11-32 | 98.0 | 55 | 180/112 | 11,000 | Neg. | No | Leg | 24 hrs. | In woods | None |
| 26 | 73775 | M | Wh. | 17 | 8- 5-32 | 99.0 | 78 | ? | 7,000 | Pus 2 plus | No | Genitals | 3 days | ? | Moderate |
| 27 | 64329 | M | Wh. | 10 | 12-12-30 | 100.0 | 90 | 114/75 | 18,000 | Neg. | No | Knee | 24 hrs. | In bed | Intense |
| 28 | 73907 | M | Wh. | 13 | 5-13-32 | 98.0 | 125 | 112/88 | 14,000 | Occ. r.b.c. | No | Knee | 3 days | Privy | Very intense |
| 29 | 69176 | M | Col. | 23 | 9-21-31 | 100.0 | 55 | 140/80 | 10,000 | Neg. | No | Genitals | 24 hrs. | Privy | Moderate |

to control his pain and cease to disturb him. All he asked for was death or relief from his agony.

Of all the series, we think this case shows more frankly than any of the others that in some instances at least a history is unobtainable and, when obtained, is worthless.

Two of our cases were bitten while in bed.

CASE 2 (70168).—An adult, awakened with a severe burning sensation in his left groin. At no time could he give us a history of having been bitten by a spider. He arose, went to the barber shop and, while sitting in the barber's chair, the usual symptoms—intense muscular cramping and generalized muscular pain—came on rather suddenly. He was sent to the hospital by an intelligent physician, with a tentative diagnosis of strangulated hernia. The man never suspected or even guessed that he had been bitten by an insect of any description.

CASE 3 (64329).—A fragile white boy, aged 10 years, was also bitten while in bed. He, however, was aware of the fact that something had stung him just above the left knee. The symptoms with him came on rapidly, and he was sent into the hospital, with a tentative diagnosis of a ruptured appendix. Again, fortunately, he was admitted to an atmosphere sympathetic to the story that he had been bitten by a spider and fully prepared to believe the almost unbelievable symptoms from which the boy suffered.

But we could very easily conceive of circumstances under which an accident of this sort could happen, where, without the educational background of the frequency of bites from the *Latrodectus mactans*, the boy's story would be disregarded, particularly in view of the fact that the evidence of the bite at the point at which it was received was negligible. The father, we are quite sure, did not believe the story at all, until he had gone home and, searching through the bed clothing, had found and brought back to the hospital the body of the female *Latrodectus mactans*.

CASE 4 (47810).—A male negro, aged 53 years, was, I believe, the most seriously sick of any of our patients. He developed a rather rapidly progressing and persistent pulmonary edema. The physician who saw him when he was admitted to the hospital suspected that he was seeing the beginning stages of a pneumonia, but subsequent events proved otherwise. This is the only case in which we have seen any evidence of pulmonary edema, and among the few which have shown any shortness of breath.

The case resembles slightly—fortunately not very closely—the case of fatal spider bite which was reported by Beasley.[5] The recovery, however, was uneventful.

Inability to void has been a fairly common symptom with us, occurring in 3 of the 29 patients. It is rather curious, however, that we have yet to see our first case of eruption following spider bite, although in the West and Southwest this appears to have been a common occurrence following the accident.

Not all of the cases of *Latrodectus mactans* poisoning resemble acute surgical emergencies most closely; one of our cases strongly suggested tetanus. It is the one case also in which we have used

glucose intravenously, with apparently some benefit. We intend to try it on future cases. The history of the case follows:

CASE 5 (73907).—A white male, aged 13 years, was sent into the hospital at 3 A.M. as an acute surgical emergency. There was a boardlike rigidity of the entire abdomen, and he was complaining of severe abdominal pain and of a cramping pain in the legs. This pain seemed to be paroxysmal in character, for he would cry out with pain at rather definite intervals. He insisted on lying on his side with the knees drawn up. The history was obtained mainly from the mother, as the patient had very little to say. He seemed to want to lie perfectly still and not be moved. At 7 o'clock the evening before, the patient had complained of pain in the knees and thighs. At 9 o'clock he was taken suddenly with severe pain in the abdomen, and this pain had continued until the time of admission. Sometime during the forenoon of the day before the patient had had a fall and suffered a rather severe bruise of the left foot, which his mother thought had to do with the symptoms. He had had no similar attacks and there was no history of any digestive disturbances of any kind. After the onset of the abdominal symptoms he was given some soda water, which was vomited, but this was not followed or preceded by any nausea. After questioning, it was found that just prior to the onset of the above symptoms the patient had visited an outside toilet and at the onset was playing in the yard. He did not remember having been bitten by anything or having seen any spider there. On admission the blood pressure was 112/88; pulse, 125; and white blood cells, 13,000.

Examination showed a poorly nourished and very anemic-looking white boy, who appeared acutely ill. The pulse was fast but of good volume; the abdomen was more rigid than we have ever seen; the back muscles were just as rigid; and the back was slightly lordotic. There was no tenderness in the abdomen even on deep pressure. The muscles of the extremities were tense but not rigid, and there was no tendency to spasm even when the patient cried out with pain. There was no abnormality of respiration. It was noted that there was a visible pulsation of the superficial veins of the arms, very much as is seen in an advanced case of arteriosclerosis with hypertension. The superficial and deep reflexes were about normal. The pupils of the eyes were dilated and reacted very sluggishly. He had had no narcotics prior to admission. Morphin, $\frac{1}{12}$ gr., was without any visible effect. Fifty cubic centimeters of 50 per cent glucose was given in the vein, and within 30 minutes the patient was sleeping. The following morning he was comfortable except for some pain in the knees, but the abdomen was as rigid as on admission. The temperature had risen to 99° F. and the pulse rate to 90. On the second day there was some relaxation of the abdominal muscles for the first time, and on the morning of the fourth day he left the hospital with a normal temperature, normal pulse and symptom-free.

**Summary.** Poisoning from the bite of *Latrodectus mactans* ("black-widow or shoe-button spider") is widely spread throughout the United States.

Inexperienced observers are apt to confuse the symptoms with those produced by an acute intra-abdominal lesion; the symptoms resemble very closely those of a ruptured gastric ulcer.

The mental symptoms lead to further confusion, as the patients are sometimes unable to give a history of having been bitten and are willing to consent to any measure which promises relief.

We have found that a certain proportion of patients are bitten while in bed, which adds still further to the difficulties of a correct diagnosis. It would be advisable to question closely all patients brought into the hospital suffering from marked rigidity of the abdominal muscles, as to the possibility of this accident having happened.

Rigidity of other large muscular masses, particularly those of the thigh and the lumbar region, is an aid in arriving at a correct conclusion.

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## DIAGNOSTIC METHODS AND METABOLIC STUDIES IN DISEASE OF THE BILIARY TRACT.

### I. Description of the Routine Examination and Discussion of Normal Standards.*

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An intensive study of diseases of the liver and biliary tract has been made possible through the organization of a specialized Gall Bladder Clinic, with a combined medical and surgical staff collaborating with bacteriologic, biochemical, and roentgenologic laboratories. All patients admitted to this clinic have been studied on a uniform schedule including history, physical examination, cholecystogram, drainage of the biliary tract with microscopic, chemical and bacteriologic analysis of the bile fractions, chemical analysis of the urine and special tests of liver function. The improvement resultant upon treatment has been evaluated by repetition of the initial diagnostic procedures. To date, 500 patients have been studied and 3000 drainages performed according to the routine schedule. Data accumulated by the chemical analysis of the blood and bile,

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obtained from these patients under uniform conditions, interpreted in the light of all clinical and other laboratory findings possess a two-fold interest both for the clinician and for the laboratory investigator. They afford (*a*) abundant material for the evaluation of such analyses as aids in diagnosis of organic and functional disturbances of the liver, gall bladder and bile ducts and often aid in a differential diagnosis of the two, and (*b*) they may serve as contributions to a better understanding of the relations of these organs to metabolism.

Such a study is needed, as any method of diagnosis may be misleading at times. The history of biliary tract disease is usually indefinite, except for the relatively uncommon symptoms of jaundice and typical colic. Physical examination is of limited value; tenderness in the right upper quadrant of the abdomen or the presence of a palpable liver or gall bladder does not necessarily lead to a correct diagnosis. Roentgenographic study cannot always demonstrate the presence of stones or explain the physiologic or pathologic changes which prevent visualization of the gall bladder. The importance of these uncertainties cannot be overestimated because of their bearing upon decisions as to the advisability of operation.

Our object here is to present our results, particularly in regard to conditions of the blood and bile in a group of 10 control subjects and 30 patients having apparently normal biliary tracts. The controls were 8 male and 2 female members of the clinic and laboratory staff, from 21 to 47 years of age, who, having had no history or clinical signs of biliary tract disease, volunteered to go through the diagnostic routine of the clinic. The 30 normals were patients, 10 males and 20 females from 24 to 63 years of age, who on admission to the clinic complained of mild types of gastro-intestinal symptoms but in whom disease of the biliary tract was excluded on the basis of all diagnostic criteria.

**Methods and Results.**—Cholecystograms were made under the direction of Dr. William H. Meyer, in all cases presented. Oral administration of the dye has been used in practically all instances, and this procedure is usually repeated if the result of the first examination is unsatisfactory. With gastro-intestinal disturbances such as vomiting or diarrhea following ingestion of the dye, or in those cases in which there are no visualizations of the gall bladder, the intravenous method of dye administration is used. Cholecystograms of the 10 control individuals revealed normal "visualization" and normal rates of evacuation of the gall bladder in all cases. Normal "visualization" of the gall bladder was observed in all of the 30 presumably normal cases. Four of these subjects exhibited a slight delay in emptying of the gall bladder in response to a meal rich in fats, which was interpreted as being probably of no significance.

For biliary tract drainage, the patient reports at 8.30 A.M. without breakfast. The general method of procedure is that described by Lyon.[1] The duodenal tubes usually used are those of the metal-tip type: the Rehfuss, Lyon, or one designed by one of the authors[2] which has the advantage in our experience of being more quickly introduced into the duodenum and more easily retained there. Duodenal intubation may be done with the

patient in the Fowler position or upright, with or without fluoroscopic guidance as described by Morgenstern.[3] The Levin catheter tip tube has also been used. Following a gastric lavage, the tube is introduced into the duodenum, according to the method described elsewhere.[4] The arrival of the tip at this point is indicated by the drainage of clear bile, the usual absence of free hydrochloric acid (as shown by Congo paper), or by fluoroscopic examination.

The first bile obtained is generally golden-yellow, this is labelled the $D_1$ specimen, as shown in Table 4. An ounce of warm 16 per cent magnesium sulphate is then injected and allowed to remain 2 minutes, the bile being obtained by syphonage. Two similar injections of 25 per cent magnesium sulphate are then used, these specimens are labelled $M_1$, $M_2$, and $M_3$. If no concentrated brown or olive-green bile is obtained in this way, an ounce of warm olive oil is instilled and allowed to remain in the duodenum 10 minutes, the resulting specimen is labelled $O_1$. Following the drainage of dark bile there is usually light yellow or lemon-yellow bile; this is called the $D_2$ specimen.

Concentrated bile was obtained in all cases of both the control and normal groups. The sediment of all bile specimens was procured by means of a pipette and examined microscopically, especially for crystals of cholesterol, calcium bilirubinate pigment, bile-stained pus cells, and columnar epithelial cells. Examination of the sediment for pathologic elements was negative in all specimens of the control subjects. The 30 normal cases were also negative microscopically except for one in whom occasional cholesterol crystals were found.

Results of the chemical analysis of the blood and bile fractions for the 40 subjects are presented in the accompanying tables. These data have been assembled for the controls and normals under conditions analogous to those for pathologic states of the biliary tract (to be presented later) and represent the normal standards and the range of variations to be expected under physiologic conditions.

Total cholesterol of whole, oxalated blood was determined by the Sackett modification of the Bloor method.[5] The control group has an average figure of 189 mg. and the normals 200 mg. per 100 milliliter of blood. Bruger and Somach[6] in a recent report upon the diurnal, physiologic variations in the cholesterol content of whole blood and of plasma of subjects in the absorptive and in the fasting state, have shown that deviations from the mean are least during the morning hours, between 9 A.M. and 1 P.M. Sackett's method has been adopted for analysis of blood and bile for cholesterol.[23] Since the specimens of blood reported in our tables were taken between 9 A.M. and 10 A.M., during a fasting state, the figures are comparable with those reported by Bruger and Somach. It is significant to note that the standard deviations for both groups, $\pm 2.8$ and $\pm 3.4$ per cent, are less than the average standard deviation of $\pm 3.9$ per cent reported by Bruger and Somach for this period of the day.

In the determination of cholesterol ester, free cholesterol was separated from the bound cholesterol by precipitation with digitonin. Similar average ratios of cholesterol esters: total cholesterol were calculated for both groups, between extremes of 0.30 and 0.69. Bloor and Knudson[7] have stated that this ratio may vary from 0.40 to 0.70.

The occurrence of bile acids in normal blood and the variations from the average normal concentration in pathologic states have been the subject of numerous reports expressing conflicting opinions within recent years. With a modification of Szilard's method, Katayama[8] found an average of 7 mg. of bile acids, as glycocholic

acid, per 100 milliliters of blood. Aldrich and Bledsoe,[9] using a quantitative Pettenkofer test, report values in normal blood equivalent to from 3 to 6 mg. of glycocholic acid for each 100 milliliters of blood. Walker[10] believes that the substance giving Pettenkofer reaction is not bile acid but probably cholesterol oleate. Perlzweig and Barron[11] found no bile acids in normal blood but obtained quantitative recoveries of added bile acids. A preliminary report by Tashiro[12] presents high figures for bile acids in the bloods of jaundiced patients but no values for normal blood. All methods employed by various analysts for bile acids in blood are based upon non-specific color reactions or precipitations, hence there is doubt about the chemical identity of the reacting substances reported as bile acids. While we await the isolation of bile acids from blood and their identification, in the interpretation of analytical results it is necessary to bear in mind that the material reacting in the analytical procedures is assumed to be bile acids only because its response to reagents is similar to that of pure solutions of the bile salts, and the analytical methods yield good recoveries of added bile salts.

The modification of the Szilard method, described by Katayama,[8] was adopted for determination of bile acids in blood and bile. In the series of 10 control subjects the bile acids calculated as glycocholic acid gave an average figure of 7.5 mg., with extremes of 19 and 3 mg., per 100 milliliters. For the 30 normal cases the average figure for bile acids was 13.6 with extremes of 22 and 3 mg. per 100 milliliters. For both series the icterus indices[13] of the serum were within the normal range, varying between extremes of 4 and 8. In the chemical analyses of blood the following procedures were used: Folin and Wu's method for sugar,[20] the aëration method described by Myers for urea nitrogen[21] and the Clark-Collip modification of the Kramer-Tisdall method for calcium.[22] For urea nitrogen of the blood, a wide range of variation was observed for both series. The average figures, however, show close agreement. The blood sugar levels for all of the cases were well within the normal limits. Also the figures for the blood serum calcium fell within the normal range. In the routine chemical analysis of the blood, determinations of the sugar and urea nitrogen were included as indices of disturbances of carbohydrate metabolism and renal function.

The results of bile analysis indicate that the average deviations found are not greater, generally speaking, than would be allowed for the experimental error in the method used. The $D_1$ bile is the clear golden-yellow bile obtained before stimulation, as previously described. A postoperative study of bile obtained by the duodenal tube simultaneously with bile obtained by means of a drainage tube in the common duct has indicated that the two specimens were similar in composition and that the factor of dilution is not of practical importance. The concentrated bile (M or O specimens) is the dark, thick, brown or olive-green bile usually obtained after repeated

stimulation; this is the "B" bile as described by Lyon. This study differs from that of McClure [14,15] in the differentiation of the various types of bile. We believe that this is important as it is always necessary to differentiate between changes in the composition of the bile which have been produced on the one hand by changes in the secretory activity of the liver and on the other hand by the contraction of the gall bladder.

TABLE 1.—RESULTS OF ROENTGENOLOGIC STUDY AND BILIARY TRACT DRAINAGE.

IN 10 CONTROL SUBJECTS.

| | |
|---|---|
| Cholecystograms taken | 10 |
| Normal "visualization"—normal emptying | 10 |
| Biliary tract drainages performed | 10 |
| Concentrated bile obtained | 10 |
| Negative microscopic examination of biliary sediment, all specimens | 10 |

IN 30 NORMAL CASES.

| | |
|---|---|
| Cholecystograms taken | 30 |
| Normal "visualization"—normal emptying | 26 |
| Normal "visualization"—delayed emptying | 4 |
| Biliary tract drainages performed* | 30 |
| Concentrated bile obtained | 30 |
| Negative microscopic examination of biliary sediment, all specimens | 29 |
| Cholesterol crystals, occasional | 1 |

* In all doubtful cases drainages are repeated.

TABLE 2.—CHEMICAL ANALYSIS OF BLOOD OF 10 CONTROL SUBJECTS.

| Constituent. | Maximum. (All values in mg. per 100 ml. blood.) | Minimum. | Average. | Average deviations. |
|---|---|---|---|---|
| Total cholesterol | 200 | 175 | 189 | ±8 |
| Cholesterol esters | 110 | 67 | 90 | ±10 |
| Cholesterol ester / Total cholesterol | 0.55 | 0.34 | 0.46 | ±0.1 |
| Bile acids as glycocholic | 19 | 3 | 7.5 | ±5.5 |
| Urea N | 14 | 7 | 11 | ±2 |
| Sugar | 93 | 70 | 83 | ±5 |
| Calcium of serum | 11 | 10 | 10.4 | ±0.3 |
| Icterus index of serum | 8 | 4 | 6 | ±1.0 |

Inspection of the bile fractions obtained by drainage in the entire series of 40 cases showed concentrated bile to be present in all cases. This finding is in agreement with the cholecystograms, assuming concentrating power of the gall bladder to be indicated by the intensity of its visualization.

In the chemical analysis of the duodenal ($D_1$) bile, cholesterol was present in sufficient amounts to be determined quantitatively in only 7 cases. Cholesterol was found in all specimens of concentrated bile, the concentration varying from a trace to 364 mg. per 100 milliliters of bile. The cholesterol content of the concentrated bile is in practically all cases distinctly higher than that of the duodenal specimens. The cholesterol content of the $D_2$ bile obtained after the concentrated specimen usually approximates that of the $D_1$ specimen.

TABLE 3.—CHEMICAL ANALYSIS OF BLOOD OF 30 NORMAL SUBJECTS.

| Constituent. | Number of analyses. | Maximum. (Mg. per 100 ml.) | Minimum. (Mg. per 100 ml.) | Average. (Mg. per 100 ml.) | Average deviations. |
|---|---|---|---|---|---|
| Total cholesterol | 30 | 294 | 153 | 200 | ±20 |
| Cholesterol esters | 23 | 147 | 56 | 95 | ±15 |
| Cholesterol esters / Total cholesterol | 20 | 0.69 | 0.30 | 0.47 | ±0.19 |
| Bile acids as glycocholic | 30 | 22 | 3 | 13.6 | ±3.4 |
| Urea N | 30 | 16 | 4 | 9 | ±2 |
| Sugar | 29 | 97 | 64 | 83 | ±9 |
| Calcium of serum | 9 | 11 | 9 | 9.8 | ±0.4 |
| Icterus index of serum | 30 | 8 | 4 | 6 | ±1.0 |

Bile acids were found in all specimens of $D_1$ bile, the average amounts for the two groups of cases being 39 mg. and 28 mg. per 100 milliliters of bile. The concentrated bile contained from 2 to 13 times the bile acid concentration of the duodenal bile.

TABLE 4.—ANALYSIS OF BILE FRACTIONS OF 10 CONTROL SUBJECTS.

| Constituent. | Bile fraction. | Maximum. (Mg. per 100 ml.) | Minimum. (Mg. per 100 ml.) | Average. (Mg. per 100 ml.) | Average deviations. |
|---|---|---|---|---|---|
| Cholesterol | $D_1$ | Trace | Trace | Trace | 0 |
| | Conc. | 92 | Trace | 51 | ±35 |
| | $D_2$ | 49 | Trace | 9 | ±15 |
| Bile acids as glycocholic | $D_1$ | 63 | 18 | 39 | ±9 |
| | Conc. | 311 | 109 | 228 | ±42 |
| | $D_2$ | 108 | Trace | 30 | ±25 |
| | Conc. / $D_1$ | 13 | 2.8 | 6.5 | ±1.9 |

The absorption of fluid and the consequent concentration of the bile by the gall bladder is generally conceded. At the beginning of our investigation the ratios of the concentration of the duodenal ($D_1$) and concentrated specimens were studied in an effort to obtain an index of gall bladder function. There are difficulties in the use of such an index because it is recognized that even though the concentrated bile arises in the gall bladder it probably is mixed with an indeterminate amount of bile from the liver in the course of the drainage. As a result the concentration ratios are less than those which we obtain by analysis of the bile removed from the gall bladder at operation. Nevertheless this study has been of value. Of particular interest is the discrepancy between the concentration ratios of cholesterol and bile acids. The average concentration ratio of cholesterol is approximately 50 and the average concentration ratio of the bile acids is about 5. These differences can be explained either as due to the absorption of bile acids by the gall bladder, as suggested by Rosenthal and Licht,[16] or to the secretion of the cholesterol by the latter viscus as suggested by Elman and Taussig[17] and Elman and Graham.[18] On the other hand Andrews and his associates state that there is no differential absorption of cholesterol and bile salts by the gall bladder wall. Unfortunately

these data deal only with the relative concentrations of the different substances concerned and so will not permit a decision between these theories.

TABLE 5.—ANALYSIS OF BILE FRACTIONS OF 30 NORMAL SUBJECTS.

| Constituent. | Bile fraction. | Number of analyses. | Maximum. (Mg. per 100 ml.) | Minimum. | Average. | Average deviations. |
|---|---|---|---|---|---|---|
| Cholesterol | $D_1$ | 19 | 41 | Trace | 7 | ±11 |
| | Conc. | 21 | 364 | Trace | 80 | ±60 |
| | $D_2$ | 8 | 104 | Trace | 17 | ±25 |
| Bile acids as glycocholic | $D_1$ | 29 | 72 | 15 | 28 | ±7 |
| | Conc. | 30 | 391 | 45 | 367 | ±66 |
| | $D_2$ | 9 | 68 | 37 | 45 | ±7 |
| | $\frac{\text{Conc.}}{D_1}$ | 27 | 12 | 1.9 | 4.9 | ±1.1 |

The concentrating power of the gall bladder as measured by the intensity of the cholecystographic shadow was found to correspond more closely to the concentration of the bile acids in the concentrated specimen than it did to the concentration of cholesterol in the same specimen.

Bacteriologic studies of the various types of bile obtained on sterile drainage have been made under the direction of Dr. Adele Sheplar. A broth culture is first made of the set to determine its sterility. Cultures and plates are then made of each type of bile. In many patients we have obtained sterile cultures consistently, or a single organism repeatedly. The results of this study are being checked in all cases coming to operation, when a culture is made of the gall bladder bile, the gall bladder wall, the cystic duct node, and of stones if present. A report will be made at a later date concerning these findings.

**Summary.** A routine of study for diseases of the biliary tract is presented with findings in 10 control individuals and 30 patients in whom a complete investigation showed no evidence of biliary tract disease.

This investigation has included: History, physical examination, cholecystogram, duodenal drainage, inspection of bile specimens, microscopic examination of biliary sediments, chemical analyses of blood and bile, icterus index determination, van den Bergh reactions and the bacteriologic study of bile.

The findings in both series of patients are presented as standards for comparison with findings in cases of suspected gall bladder or liver disease.

Results indicate that with a normally functioning biliary tract these tests should show:

(*a*) A satisfactory "visualization" of the gall bladder on roentgenographic study.

(*b*) The presence of 30 to 60 milliliters of concentrated bile during non-surgical biliary tract drainage.

(*c*) The absence of pathologic elements on microscopic examination of the biliary sediment in all specimens.

(*d*) Little or no cholesterol in the $D_1$ and $D_2$ bile.

(*e*) Bile acids of the concentrated bile fraction 4 to 7 times greater than that of the duodenal bile.

(*f*) The absence of pathogenic organisms which occur repeatedly in bile obtained by sterile duodenal drainages.

(*g*) A blood serum icterus index reading of 4 to 8, a negative direct van den Bergh reaction.

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## GALACTOSE TOLERANCE AS A MEASURE OF LIVER FUNCTION.

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Galactose tolerance was first proposed as a liver function test by Bauer[1] in 1906. As extensive reviews of the literature on this test have been published, reference to the earlier work upon this subject need not be made. In this test, as it is most widely used,

40 gm. of galactose is given by mouth and the galactose excreted in the urine during a 5-hour period following ingestion is determined. If the urinary galactose for the 5-hour period exceeds 3 gm., it is considered evidence of hepatic insufficiency. Recently studies of the total blood-sugar concentration and the degree of galactosuria following galactose ingestion have been made by Machold,[2] Bode,[3] and Pollak.[4] The determination of the total blood sugar following galactose administration does not give specific information regarding the amount of galactose in the blood, hence we thought it of interest to study the blood galactose concentration following galactose ingestion in normal subjects and in patients with representative types of liver damage.

In beginning our work it seemed important to establish a uniform dosage of galactose. The arbitrary use of a fixed dosage of galactose for all patients, regardless of size, did not seem satisfactory, because of the differences in the amounts of intestinal absorptive surface and of liver and muscle tissue in subjects of varying sizes. We, therefore, adopted the use of 1 gm. of galactose per kilogram of body weight as a dosage which we believe gives more comparable results than the arbitrarily established 20- to 40-gm. amounts that have been used by different workers.

The procedure used by us for the studies of this report is as follows: The test is carried out under fasting conditions, usually in the morning. A control sample of blood is obtained and galactose dissolved in a convenient quantity of water is given by mouth. Blood samples are collected ½ hour, 1 hour and 2 hours after ingestion, and a single urine sample is collected at the end of the 2-hour period. The galactose content of the blood and urine samples is then determined. The blood galactose is estimated by the method developed by ourselves.[5] The urinary galactose is determined by titrating against Benedict's quantitative copper solution, 1 cc. of which is reduced by 0.0025 gm. of galactose. In order to obtain a study of the relation between the total sugar of the blood and the blood galactose following galactose ingestion, we also determine the total blood sugar by Benedict's method.[6]

A study of the galactose tolerance of 10 normal subjects by the procedure described above was recently made by us.[5] In Table 1 a part of our data is reproduced, to show the relation of the concentration of galactose in the blood to the amount of galactose excreted in the urine. It has been generally claimed that the kidneys do not maintain a threshold for galactose excretion and hence the part played by the kidneys has no significance in the interpretation of the degree of galactosuria obtained following galactose ingestion. The evidence obtained by us does not agree with this conception. The data of Table 1 show that the amount of galactose in the urine does not parallel the levels of galactose in the blood. This evidence indicates that the kidneys maintain a threshold for galactose excre-

tion which varies considerably in normal subjects. This is well illustrated by subjects H. D. and J. R., who received essentially the same dose of galactose. With subject H. D., the highest blood galactose obtained was 80 mg. per 100 cc. and the urinary galactose was 0.91 gm. With subject J. R., the highest blood galactose was 63 mg. per 100 cc. and the urinary excretion was 2.48 gm. Subjects G. R. and A. S. present a like contrast. With subject G. R. we obtained the highest blood galactose of our series, 138 mg. per 100 cc., and the urinary galactose of this subject was 1.75 gm. With subject A. S. we obtained the next to lowest blood galactose in our series of 10 subjects, which was 39 mg. per 100 cc., and the urinary galactose was 2.25 gm. Similarly other contrasts may be drawn from this table. These data show the existence of a galactose kidney threshold which varies in different subjects, just as the kidney threshold for glucose excretion varies.

TABLE 1.—GALACTOSE TOLERANCE OF NORMAL SUBJECTS.

(From the Data of Roe and Schwartzman, J. Biol. Chem., 1932, **96**, 717.)

| Subject. | Sex. | Galactose ingested (gm.). | Galactose in 2-hour urine sample (gm.). | Blood galactose (mg. per 100 cc.). | | | |
|---|---|---|---|---|---|---|---|
| | | | | Control (saccharoid). | ½ hr. | 1 hr. | 2 hrs. |
| H. D. | F. | 74 | 0.91 | 7 | 28 | 80 | 34 |
| C. S. | F. | 44 | 0.92 | 7 | 90 | 109 | 34 |
| A. M. | M. | 66 | 1.00 | 8 | 29 | 37 | 32 |
| R. E. | M. | 64 | 1.00 | 9 | 32 | 67 | 30 |
| F. B. | F. | 60 | 1.35 | 10 | 53 | 100 | 29 |
| G. R. | M. | 70 | 1.75 | 10 | 67 | 138 | 101 |
| E. B. | F. | 58 | 2.20 | 9 | 53 | 89 | 118 |
| A. S. | M. | 61 | 2.25 | 7 | 35 | 39 | 36 |
| J. R. | M. | 75 | 2.48 | 9 | 56 | 63 | 33 |
| G. Y. | F. | 59 | 2.78 | 11 | 80 | 120 | 106 |

From our studies with normal subjects we came to the conclusion that better evidence is obtainable concerning the functioning of the liver by determining the circulating level of galactose in the blood than by determining the urinary galactose excretion, although the estimation of both of these is of interest.

The results of our studies of 17 cases of liver disease are summarized in Table 2, and are shown graphically by the curves of Fig. 1. In the cases of cirrhosis, metastatic carcinoma, passive congestion due to heart failure, and toxic or chronic degenerative hepatitis, the blood galactose curves and the urinary galactose excretion are well within the limits obtained with 10 normal subjects. These cases do not show any evidence of reduced galactose tolerance and they indicate that the galactose tolerance liver-function test may not be expected to give evidence of diagnostic value in the types of liver disease of which they are representative. This is especially indicated by C. S., a case of severe portal cirrhosis with ascites. In this case there was marked bilirubin retention and the bromsulphalein test showed 90 per cent retention of dye in the 30-

TABLE 2.—GALACTOSE TOLERANCE OF CASES WITH LIVER DISEASE.

| Subject. | Sex. | Galactose ingested, gm. | Blood sugar, mg. per 100 cc. | | | | | | | | Galactose in 2-hr. urine sample, gm. | Diagnosis. | Method of diagnosis. | Other data.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Galactose. | | | | Total sugar as glucose. | | | | | | | |
| | | | Control. | ½ hr. | 1 hr. | 2 hrs. | Control. | ½ hr. | 1 hr. | 2 hrs. | | | | |
| C. S. | M. | 90 | .. | 38 | 41 | 29 | ... | 154 | 148 | 128 | 1.91 | Cirrh. with ascites | Aut. | J.; bili., 21 mg. per 100 cc.; I. I., 150; Bs., 90% retention. |
| J. J. | M. | 65 | 8 | 31 | 63 | 28 | 70 | 92 | 129 | 105 | Trace | Atrophic cirrh. | Clin. | |
| M. S. | F. | 73 | 5 | .. | 45 | 47 | 80 | ... | 110 | 98 | .... | Banti's dis. | Clin. | |
| R. A. | M. | 48 | 5 | 17 | 12 | 15 | 73 | 73 | 74 | 88 | .... | Metast. carc. liver | Biop. | |
| C. G. | M. | 50 | 10 | 20 | 28 | 31 | 81 | 93 | 103 | 109 | .... | Metast. carc. liver | Biop. | J. |
| S. G. | M. | 48 | 5 | 21 | 30 | 33 | 52 | 63 | 88 | 88 | 0.10 | Metast. carc. liver | Clin. | J.; bili., 7.1 mg. per 100 cc. |
| J. W. | M. | 60 | 9 | 32 | 96 | 47 | 62 | 79 | 139 | 97 | 0.75 | Cong. ht. failure | Clin. | |
| F. B. | F. | 70 | 8 | 23 | 29 | 28 | 83 | 110 | 101 | 112 | 0.12 | Cong. ht. failure | Clin. | |
| E. T. | M. | 75 | 11 | 32 | 61 | 69 | 80 | 96 | 109 | 103 | Trace | Cong. ht. failure | Clin. | Bs., 25% retention; bili. normal (6 days after galactose test). |
| P. H. | F. | 50 | 7 | 22 | 93 | 115 | 70 | 85 | 123 | 152 | 1.10 | Tox. degen. hepatitis | Clin. | Bili., 0.8 mg. per 100 cc.; I.I., 50; Bs., neg. |
| D. L. | F. | 50 | 4 | 17 | 30 | 56 | 68 | 84 | 93 | 109 | 0.52 | Chr. degen. hepatitis | Clin. | Bili., 1 mg. per 100 cc. |
| W. P. | M. | 63 | 9 | 38 | 81 | 125 | 85 | 112 | 130 | 167 | 0.71 | Chr. degen. hepatitis | Clin. | J.; bili., 20 mg. per 100 cc.; I.I., 160. |
| M. R. | F. | 65 | 10 | 10 | 16 | 13 | 111 | 95 | 105 | 113 | Trace | Cholelith. | Oper. | J.; bili., 6.7 mg. per 100 cc.; I.I., 90. |
| A. M. | M. | 65 | 10 | 98 | 143 | 21 | 82 | 135 | 167 | 94 | 3.00 | Ac. catar. J. | Clin. | J.; bili., 15 mg. per 100 cc.; I.I., 83; Bs., 25%. |
| A. M. | F. | 50 | 8 | 51 | 125 | 230 | 74 | 102 | 150 | 222 | 1.48 | Ac. catar. J. | Clin. | J.; bili., 11.2 mg. per 100 cc.; I.I., 150. |
| A. B. | M. | 50 | 4 | 68 | 123 | 39 | 67 | 105 | 156 | 94 | 0.75 | Ac. catar. J. | Clin. | J.; bile in urine. |
| B. C. | F. | 73 | 9 | 41 | 122 | 143 | 79 | 111 | 159 | 197 | 0.78 | Ac. catar. J. | Clin. | J.; bili., 10.3 mg. per 100 cc.; I.I., 100. |

* J. = jaundice; bili. = bilirubin; I.I. = icterus index; Bs. = bromsulphalein.

minute sample, yet the blood-galactose curve was that of a low normal. In the other cases of chronic liver disease there was shown a similar lack of sensitivity of the galactose tolerance test as compared with other tests for liver damage.

In 4 cases of catarrhal jaundice the blood galactose reached a level which was either around that of our highest normal case or was considerably above that of our normal subjects. In catarrhal jaundice then one may expect to find evidence of reduced galactose tolerance and the galactose tolerance liver-function test here may be of diagnostic value. In contrast with the high values obtained in catarrhal jaundice, the low blood-galactose curve and reduced urinary galactose excretion obtained with M. R., a case of cholelithiasis with

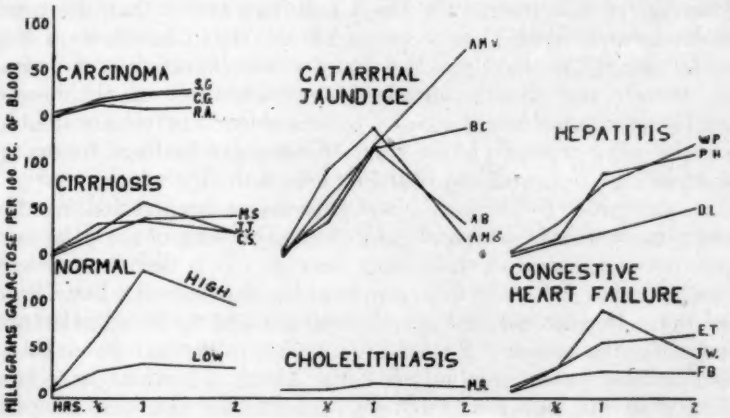


FIG. 1.—Blood-galactose curves of cases with liver disease. (From the data of Table 2.)

marked jaundice, show that the galactose tolerance test may be of considerable value in the differential diagnosis of obstructive jaundices of infectious and non-infectious origins. These conclusions are in agreement with the report of Shay, Schloss and Rodis,[7] who obtained their evidence by studies of the urinary galactose excretion only.

In general the data obtained by us with 17 cases of liver disease indicate that in chronic liver disease one may not expect to obtain evidence of functional disturbance of the liver by the galactose tolerance test unless very severe and widespread liver damage exists. This is apparently because in chronic liver disease the regeneration of functional liver tissue is usually rapid enough or the margin of safety great enough to provide for the carbohydrate metabolism of this organ. The test may be of value, however, in acute liver disease. In cases of acute liver lesions, such as catarrhal jaundice, the onset of the disturbance is rapid; consequently the

capacity of the liver to metabolize carbohydrate is reduced and evidence of this disturbance may be obtained by the galactose tolerance liver-function test.

The total blood sugar following galactose ingestion was determined in order to study the relation between the total blood sugar and the blood galactose. In general the total blood-sugar curves parallel the blood-galactose curves in the cases of liver disease which we studied and no additional information was obtained by estimating the total blood sugar. From our experience we recommend a procedure in which only the blood galactose is estimated, as this is as simple as that of the total blood-sugar determination, and the blood-galactose concentration is a more specific indication of the capacity of the liver to metabolize galactose. An additional advantage of determining the blood galactose rather than the total blood sugar, as others have recommended, is that the collection of a control sample of blood previous to galactose ingestion is unnecessary, thereby reducing the number of venipunctures. As the dosage used by us differs from that used by other workers, we are unable to make comparisons of our total blood-sugar findings following galactose ingestion with any of the reports in the literature.

In our studies the highest blood-galactose concentration usually came 1 hour after ingestion of galactose. The peak of the galactose curve never occurred at the ½-hour interval. It is therefore useless to estimate the galactose in a sample of blood collected ½ hour after ingestion. Occasionally the greatest elevation of the blood galactose occurred in the sample collected 2 hours after ingestion. From these observations we recommend that the blood collection procedure followed in this paper be modified and that for this test samples of blood be taken at 1-hour intervals for 3 hours following galactose ingestion. The collection of a control sample of blood is obviously unnecessary, as there is no galactose in fasting blood.

From our studies the following interpretations are suggested regarding the proposed galactose tolerance liver-function test, in which 1 gm. of galactose per kilo of body weight is given by mouth under fasting conditions:

1. A galactosemia in excess of 150 mg. per 100 cc. of blood following the ingestion of galactose, in the presence of supporting clinical evidence, is pathognomonic of liver disease.

2. Blood-galactose values between 125 and 150 mg. per 100 cc. of blood at the peak of the galactosemia must be considered as borderline values. In the presence of supporting clinical evidence such values may be taken as evidence of reduced liver function. Normal subjects, however, may be expected occasionally to show blood-galactose values within, or possibly slightly above, this range following the ingestion of the designated dosage of galactose.

3. Blood-galactose values below 125 mg. per 100 cc. of blood must be considered as a normal response following the ingestion

of the proposed dosage of galactose, but should not be regarded as eliminating liver disease.

**Summary.** 1. A study of the galactose tolerance of normal subjects and patients with representative types of liver disease has been made by determining the blood and urinary galactose concentration following the ingestion of galactose by mouth. Data are presented showing that following galactose ingestion, the blood-galactose concentration is a better indication of liver function than the urinary galactose excretion since it is not influenced to the same extent by a variable renal threshold.

2. Blood-galactose concentrations similar to those of normal subjects were obtained in cases of cirrhosis, metastatic carcinoma, congestive heart failure, toxic and chronic degenerative hepatitis. The urinary galactose excretion in these cases was essentially the same as observed in normal subjects. These studies indicate that the galactose tolerance liver function test may not be expected to give evidence of diagnostic value in chronic liver disease.

3. Blood-galactose values higher than normal were observed in cases of acute catarrhal jaundice. A normal response was obtained in a case of cholelithiasis with marked jaundice. These findings indicate that the galactose tolerance liver function test may be of value in the differential diagnosis of jaundices of infectious and non-infectious origins.

4. Based upon these studies a new technique for the galactose tolerance liver-function test is proposed. In this test 1 gm. of galactose per kilo of body weight is given by mouth under fasting conditions and the galactose content of samples of blood collected at hourly intervals for 3 hours following ingestion is determined. Data are presented for the interpretation of findings obtained by this technique.

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# REVIEWS.

A Dictionary of Greek and Latin Combining Forms Used in Zoological Names. By Edmund C. Jaeger, Head of the Department of Zoölogy, Riverside Junior College, Riverside, Calif. Pp. 157. Second edition. Springfield, Ill.: Charles C Thomas, 1931. Price, $1.50.

The amusement that the layman often gets out of apparently cumbersome scientific names should cause no embarrassment to the scientist who realizes that the single word may carry a wealth of meaning within its polysyllables. With the regrettable decadence of knowledge of Latin and Greek, however, this advantage is being more and more lost, and a dictionary such as this becomes correspondingly more and more valuable. Though the more than 2000 words here included contain much of medical interest, we are churlish enough to wish that it had been further extended in scope and content. This remark is intended to serve also as a compliment to the producers on the success of their undertaking. E. K.

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Sex and Internal Secretions. By various contributors. Edited by Edgar Allen, University of Missouri. With a Foreword by Robert M. Yerkes, Yale University. Pp. 951; illustrated. Baltimore, Md.: The Williams & Wilkins Company, 1932. Price, $10.00.

This volume is really a series of 19 reviews, broadly covering the question of sex and endocrines, by 21 American authors selected for their competence and authority. The subjects presented include: genetics, and the interrelationship of genic and endocrine factors; embryologic foundations of sex in vertebrates; sex deviations and inversions; metabolism of sex; the control of plumage in birds; histologic changes in the pituitary; ovulation, and the transport of ova and sperm; the physiology of the mammary gland; the biology and chemistry of the secretions of the ovary, testis and pituitary; the biologically active substances of pregnancy urine, including a discussion of pregnancy tests; and, finally, endocrine disorders in man. It is probably true that no one man could have written this volume, so broad is its scope; likewise is it highly probable that no one man could reivew this entire work adequately. For this reason alone this volume should prove to be of great value to all biologists interested in sex in its broadest sense. It is doubtful if even the most learned student in the field could read this book without learning much of value to him, much that he would like to know . . . and did not.

In the words of the editor, it was the purpose of this coöperative effort "to survey the most important recent researches in problems of sex, especially those concerned with internal secretions, in order that the concepts already established by experimental evidence may be clearly stated and made easily available." It is readily apparent that this purpose has been handsomely fulfilled. Each of the 19 chapters is singularly well written, the subject matter being clearly and tersely stated. The chapters dealing with material familiar to the Reviewer adequately cover the field, the one

exception being the chapter on the corpus luteum. Here the discussion is limited to the work with corpus luteum extracts, and this is unfortunate in so far as some of the most important and thought-provoking work on the corpus luteum has been omitted or given scant notice. Through skillful editing duplication of material by the several authors has been avoided, and helpful cross-references guide the reader to a fuller discussion of any point cited by more than one author.

One adverse criticism concerns the limitation of space and emphasis devoted to controversial matter, and to those stubborn facts which do not fit prettily into any hypothesis that can at present be formed from the bulk of the material at hand. More emphasis here would have produced a volume much more challenging to thought and provocative to further research, though we recognize that it might have expanded the material to a mass too unwieldly for one volume. Because it is one volume, and because it contains between its covers so much of our present knowledge of sex and endocrines, herein lies its chief value. With the full bibliographies at the end of each chapter, and the excellent author and subject indices, it should be an indispensable reference work. For the average physician this book would probably not be a prudent investment; it contains much that would not interest him and too much of that which would interest him. It is the gynecologist and the obstetrician who will find profit in this volume. Those who seek to keep abreast of the times will find it a comforting guide to the important developments which in this field have come so rapidly as to bewilder even the investigators. M. F.

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CASE STUDIES IN THE PSYCHOPATHOLOGY OF CRIME. By BEN KARPMAN, M.D., Psychotherapist, St. Elizabeth's Hospital; Professor of Psychiatry, Howard University, Washington, D. C. Pp. 1026; 14 charts. Washington, D. C.: Mimeoform Press, 1933. Price, $12.00.

IN the 5 case reports constituting this volume, the author has endeavored to embody all available information bearing upon the psychogenetic elements conducive to criminality. Each obvious physical ailment was given appropriate attention, after which treatment was psychoanalytic.

One must differ from the writer in saying "criminals are sick people." A bad man is not necessarily a sick man. Often he appears just vicious—showing atavism—reversion to an earlier type. The volume is unique and its value would be enhanced by condensation and perhaps by such phraseology as would relieve it of seeming obscenity, thereby overcoming those legal restrictions necessarily placed upon the distribution of such literature. This has been achieved by Havelock Ellis and other writers. Few readers know the meaning of "punk," "wolf" and "stir-wise," hence a brief glossary giving the prison vernacular would be helpful. N. Y.

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PRACTICAL HEMATOLOGICAL DIAGNOSIS. By O. H. PERRY PEPPER, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and DAVID L. FARLEY, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine at the University of Pennsylvania. Pp. 582; 3 plates of colored illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $6.00.

THE dearth of good works on hematology in English is largely filled by this welcome work. Still more, the authors' aim of "presenting the prac-

tical aspects of clinical hematology in simple terms" has been so well achieved that we now have something different than just another good text-book. The efficiency of composition and exceeding clarity of exposition—not usually strong points in American text-books—stand out to such a degree that the book might well be studied to advantage by those contemplating text-book production. Part I, comprising almost half the book, deals with the blood cells, methods of study and significance of results. Part II, the shortest section, deals with specific disorders of the hemolytopoietic system. Part III (159 pages), presents in concise but adequate form the hematologic findings of some 400 diseases not primarily of the blood. This feature, which is unique, as far as the Reviewer is aware, should be of especial use to the general practitioner. Where the general standard is so high, we can well afford to forebear from mentioning the occasional items that might have been improved. We predict a useful and honorable career for this very practical addition to hematologic literature. E. K.

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CHAPTERS IN AMERICAN OBSTETRICS. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University School of Medicine. Pp. 90; 10 plate illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $2.00.

PROMPTED by the desire to learn and describe "Something of the contributions of American physicians to obstetrics," the author has gathered together interesting material on the colonial midwifery system and on Shippen, James Lloyd, Bard, John Stearns, Dewees, Oliver Wendell Holmes, M. B. Wright and Walter Channing. The first obstetrical teaching, the first American textbook, "pulvis parturiens," difficult parturition, the contagiousness of puerperal fever, cephalic version, etherization in childbirth and the anemia of pregnancy are topics which one naturally looks for and finds. The only criticisms that arise are about the relatively high price and regret that the text is not twice as long. E. K.

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PAPERS RELATING TO THE PITUITARY BODY, HYPOTHALAMUS AND PARASYMPATHETIC NERVOUS SYSTEM. By HARVEY CUSHING, Professor of Surgery (Emeritus), Harvard University; recently Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 234; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $5.00.

OUR knowledge of the pituitary, the most inaccessible and perhaps the most complicated of the endocrine glands, has been changing and expanding rapidly in recent years, due in no small measure to the author's own contributions. This expansion of 4 lectures delivered in 1930–1932 is an accurate, thoughtful and suggestive statement of these advances, though, as the author is the first to recognize, "it is quite probable that many of the interpretations are based on false premises and that even those which appear to be more securely grounded will not stand the test of time." In fact, some might well have already been modified: The Camus-Roussy and Bailey-Bremer doctrine of polyuria production by tuber cinereum lesions, for instance, without regard to the intrinsic defects in their evidence seems sufficiently negated by the line of thought here presented to have been given its historical value only. Although the mode of presentation adopted necessarily produces overlaps and occasional demoded statements, the latter at least have been well take care of by textual or footnote insertions between square brackets. Most interesting in the book, as always, is the author's unique style, with its skillful use of the historical approach, its clarity of picturesque diction and pleasant inter-

ruptions with appropriate generalizations. Even his *confessio* of frank belief in teleology in nature is done with minimal irritation. Most important in the subject matter is the bulk of the first lecture, deriving from the tangle of contradictory evidence about the three pituitary lobes and their diencephalic connections a logical and convincing statement (summarized on page 57) about the functions involved. The lecture on the basophilic adenomas (lesions first described by Erdheim in 1903) puts this latest pituitary syndrome squarely on the map. As a clinicopathologic description, it leaves little to be desired. The physiologist, neurosurgeon, endocrinologist and intern can no better afford to be without this book's help than the surgeon can do without his textbook of anatomy.

E. K.

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A CRITIQUE OF SUBLIMATION IN MALES: A STUDY OF 40 SUPERIOR SINGLE MEN. By W. S. TAYLOR, Professor of Psychology, Smith College. Pp. 115. Worcester, Mass.: Clark University Press, Genetic Psychology Monographs, 1933. Price, $2.00.

THE author's effort has been to test the validity of the psychoanalytic theory of "sublimation," which, as he understands it, is the turning of "sex energy" from its natural outlet into intellectual, artistic and other "higher channels." This, it is alleged, has been done by some artists, philosophers and saints.

Accepting the theory in its entirety, only physically able, socially normal and mentally superior men were selected for questioning. The answers submitted by each individual showed an unsublimated quantum of sex expression in one or more forms, termed "adjustment." The several "adjustments" were: nocturnal emissions, erotic fondlings ("spooning," "necking" and "petting"), masturbation and resort to prostitutes and other women. The sex expression in order of frequency was as follows: masturbation, nocturnal emissions, erotic fondlings, prostitutes and women other than prostitutes. It is admitted that this analysis has not yielded finality.

Support is lent to the old faith in early marriages. In college, young married couples appear to be more contented and more successful. Economically, "if it is not true that two can live as cheaply as one, it is nevertheless true that two can live as cheaply as two."

N. Y.

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CLINICAL PHYSIOLOGY OF THE EYE. By FRANCIS HEED ADLER, M.A., M.D., F.A.C.S., Instructor in Physiology and Ophthalmology, Medical School, University of Pennsylvania; Assistant Surgeon, Wills Hospital. Pp. 406; 92 illustrations. New York: The Macmillan Company, 1933. Price, $5.00.

THIS book fulfills a need: before its appearance there was not available a text in the English language on the physiology of the eye sufficiently extensive to be of use to both the physiologist and the practising ophthalmologist. The author, who has happily combined the clinical aspects of ophthalmology with the experimental side of the physiology of the eye, is peculiarly qualified to write such a book. As he states in the introduction he has endeavored to write "a small textbook, giving in as simple terms as possible the fundamental facts and generally accepted theories of how the eye functions." The Reviewer believes that the author has fully accomplished his purpose.

The table of contents, better than further general discussion, may best convey the scope of the book. There are chapters on the protective

mechanism of the eye, the iris and pupil, accommodation, the lens and vitreous, visual acuity, visual pathways and visual fields, the objective changes in the retina due to light, the subjective characteristics of vision, binocular vision, entoptic and allied phenomena, the optic nerve, external ocular muscles, aqueous humor and the intraocular pressure. At the end of each chapter there is a very useful list of references to guide the reader who would pursue the subject further. The illustrations, many of them simple diagrams, are a valuable addition to the text. The style is clear and readable. This book will be welcomed by all who in practice or research are interested in the function of the eye under normal and pathologic conditions. B. L.

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CRIMES AND CRIMINALS. By WILLIAM A. WHITE, A.M., M.D., Sc.D. Pp. 276. New York: Farrar & Rinehart, 1933. Price, $2.50.

AFTER 40 years' practice in psychiatry with intimate contact with the criminal insane, the writer complains of the inadequacy of the law to meet the requirements of criminology and, among other reforms, recommends abolition of capital punishment. Clarence Darrow goes farther and asks that all prisons be done away with. In the past, Russia, Austro-Hungary and a part of Italy abandoned capital punishment but all returned to it later. In this country the maximum punishment is exacted with less and less frequency and our criminal population is constantly growing. The author was more familiar with criminals who were insane than with those who were not; he should observe the convicts during a prison riot.

In wars millions of good men are obliged to march to one another's destruction, and if it is right—or under the circumstances necessary—to kill so many good men, it cannot be entirely wrong to kill a few bad ones. The eminently sound and kindly William Howard Taft was right when he said: "We are pampering our criminals." An intellectual criminal once remarked to the Reviewer: "That there is honor among thieves is the one good joke accredited to the underworld." N. Y.

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THE GOLD-HEADED CANE. By WILLIAM MACMICHAEL, M.D. Edited with Explanatory and Illustrative Notes and an Essay on William MacMichael, M.D., His Life, His Work and His Editors by HERBERT SPENCER ROBINSON. Pp. 223; illustrated. New York: Froben Press, Inc., 1932. Price, $5.50.

THIS is the 6th and latest edition of that celebrated account of the passage of the cane through the hands of five of England's most famous physicians. A portrait, biography and bibliography of the author together with specimens of his handwriting add considerably to the interest of this edition. E. K.

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THE TIDES OF LIFE: THE ENDOCRINE GLANDS IN BODILY ADJUSTMENT. By R. G. HOSKINS, PH.D., M.D., Director of Research, Memorial Foundation for Neuroendocrine Research; Research Associate in Physiology, Harvard Medical School. Pp. 352; illustrated. New York: W. W. Norton & Co., Inc., 1933. Price, $5.50.

FOR some years it has become increasingly apparent that the control of the body exerted by the endocrines in health and disease is of constant and utmost importance. The dramatic nature of endocrine disorders and of endocrine therapy and the complexity of their interrelationships, however, have led to so much romance in endocrin literature that skepticism

has encouraged and more than one conservative scientist repelled into other fields. A restrained statement such as the present one, accurately and ably compiled by a master student of endocrinology, is therefore to be welcomed as an especially important contribution. Its eliability can safely be guaranteed and on points where our knowledge is still hazy the author makes sure to point this out. Though written clearly and with excellent selectivity, the subject from its very nature will not furnish easy reading for the general reader. To those who are willing to bend their energies to its mastery, the reward will be considerable.

E. K.

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HOEBER'S SURGICAL MONOGRAPHS. THE DUODENUM. ITS STRUCTURE AND FUNCTION, ITS DISEASES AND THEIR MEDICAL AND SURGICAL TREATMENT. By EDWARD L. KELLOGG, M.D., F.A.C.S., Professor of Surgery, and Formerly Professor of Gastro-enterology, New York Polyclinic Medical School, etc. With a Foreword by GEORGE DAVID STEWART, M.D., F.A.C.S., New York. Chapter on Duodenal Parasites by BAILEY K. ASHFORD, M.D., Sc.D., Professor of Tropical Medicine and Mycology, University of Puerto Rico and Columbia University, New York, etc. Section on Roentgen Ray Diagnosis by A. JUDSON QUIMBY, M.D., Professor of Roentgenology, New York Polyclinic Medical School. Pp. 855; 287 illustrations, 3 in color. New York: Paul B. Hoeber, Inc., 1933. Price, $10.00

THE delightful foreword to this monograph was written by George David Stewart, whose unfortunate death has just occurred. The author, who has for some years been making contributions to the subject of this book, has here for the first time in English dealt thoroughly with the anatomy, physiology, bacteriology and various diseases of the duodenum, as well as their treatment. There are 131 pages of references which is the most complete bibliography which the Reviewer has seen. The illustrations are numerous and excellent. Of the twenty-six chapters, the chapter on Physiology was written by Professor A. C. Ivy, while Dr. F. M. Jefferies prepared the text dealing with laboratory procedures.

While it may be considered by some that this is purely a monograph for surgeons, since it is one of a series of surgical monographs, it covers the medical diseases of the duodenum thoroughly. The author does, however, suggest rectal feeding in the treatment of duodenal ulcer, disregarding recently published data to the effect that this method is of little practical significance. He also omits the Andresen diet for bleeding duodenal ulcer. These are, however, small errors when one looks at the book as a whole.

The subject matter on duodenal ulcer is presented fairly and without bias, even though the author is a surgeon! I am sure that this monograph will be well received. It will remain for years to come as a classic on its subject. There will be few internists, specialists, or surgeons who will want to be without it.

I. R.

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INTERNATIONAL CLINICS. VOL. I, FORTY-THIRD SERIES, MARCH, 1933. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, with the collaboration of twelve associates. Pp. 305; 16 illustrations, 1 colored plate. Philadelphia: J. B. Lippincott Company, 1933. Price, Cloth, $3.00.

THIS volume is the first of a new series appearing after a complete reorganization with a new editor and a new list of collaborators, all prominent

medical names of this country, Canada and abroad. The object of International Clinics of bringing to the practitioner in the form of clinics, clinical lectures and reviews the latest information about current medical thought and practice, will be well attained if the standard of excellence of the present volume is maintained. The names of the new editor and his 12 collaborators should guarantee this maintenance, if their contact continues to be an active one. Although the title page continues to advertise "by leading members of the medical profession throughout the world," we note that only two of the collaborators are not of this continent and all of the 19 articles are by Americans. Though excellence is to be preferred, regardless of origin, we hope that the former international character of the journal will be retained. E. K.

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PROCEDURES IN TUBERCULOSIS CONTROL FOR THE DISPENSARY, HOME AND SANATORIUM. By BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois; Formerly Medical Director and Member and Secretary, Board of Directors, City of Chicago Municipal Tuberculosis Organization. With a Chapter on Sanatorium Planning by THOMAS KIDNER, New York City, and an Introduction by DAVID J. DAVIS, M.D., PH.D., Dean of the College of Medicine, University of Illinois, Chicago. Pp. 373; 54 illustrations. Philadelphia: F. A. Davis Company, 1933. Price, $4.00.

TUBERCULOSIS is here considered from the viewpoint of the public health official. Measures used to prevent the transmission of this disease, especially those adopted in Chicago, are described. In the first section there are chapters on special tuberculosis problems such as disease in the Negro and the Mexican; on tuberculosis legislation; and on establishment and operation of tuberculosis dispensaries, examination of contacts, epidemiological surveys, etc. The second section deals with the factors involved in the successful treatment of tuberculous patients in their homes. It is recognized that the sanatorium can accommodate only a small percentage of those who need treatment. In the third section there is a very complete discussion of the establishment and operation of tuberculosis sanatoria, sanatorium treatment and convalescent care.

This book is of little value to the student seeking to learn the symptoms, physical signs, differential diagnosis and treatment of pulmonary tuberculosis. But to social service and public health workers interested in the control of tuberculosis, it can be well recommended. H. H.

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CHRONIC ARTHRITIS AND FIBROSITIS. By BERNARD LANGDON WYATT, M.D., F.A.C.P., Director, The Wyatt Clinic, etc. Pp. 201; 17 illustrations. Baltimore: William Wood & Co., 1933. Price, $3.50.

THIS little book is chiefly a collection of the studies and views of others. The text consists, in large part, of actual citations taken from original articles and various standard works. To the extent that the book reflects the increasing interest being shown in the field of arthritis it may serve a useful purpose. It further reflects, to some degree, the wider-angled outlook upon the subject now undeniably gaining ground.

Therefore to those unfamiliar with the rheumatoid syndrome, it may serve as an introduction. To the critical observer the book plainly reveals a purely clinical experience in this field and the author makes the mistake of introducing a classification of his own, rather than accepting the almost

universally adopted separation of chronic arthritis, based on morphologic data, into two groups, atrophic and hypertrophic. The type is good and the book is light in weight, a feature all too rare in American publications.

R. P.

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DISEASES OF THE HEART. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., HON. D.Sc. (MICHIGAN), Physician in Charge of Department of Clinical Research, University College Hospital, London, etc. Pp. 297; 44 illustrations. New York: The Macmillan Company, 1933. Price, $3.50.

THE success of the author's small books on Clinical Electrocardiography and Clinical Disorders of the Heart Beat clearly indicated that a similar book on general diseases of the heart would and should be forthcoming. In the present work common forms of heart disease and the information to be gained from physical signs have been stressed; a laudable purpose that has been aided by the rather novel arrangement, based more on disordered function than on structure. Thus after several chapters on the signs of cardiac failure, their cause, detection, significance and treatment, 2 short chapters follow on coronary thrombosis and angina pectoris. The disorders of mechanism are condensed into 34 pages and heart block combined with syncope. Rheumatic heart disease occupies 17 pages, compared to 6 of congenital malformations; while syphilis has 14, compared to 11 of pericarditis. Such condensations necessarily involve penalty; thus we find no mention whatever of tuberculous pericarditis; though a full page is given to Persistent Ductus Arteriosus, Fallot's Tetralogy and the useful grouping of congenital cases according to absent, tardy or constant cyanosis are conspicuous by their absence. While such omissions should not militate against a book which will undoubtedly be of great service and popularity, we cannot help but exclaim—a little more, and how much better! E. K.

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FOOD IN HEALTH AND DISEASE. By KATHERINE MITCHELL THOMA, B.A., Director of Dietetics, Michael Reese Hospital, Chicago. Pp. 370. Philadelphia: F. A. Davis Company, 1933. Price, $2.75.

THIS book is for student nurses and others interested in dietetics. Of its four parts, Part I is devoted to food and food requirements of normal individuals; Part II to diets in disease; Parts III and IV contain laboratory lessons for the study and preparation of various foodstuffs for the well and sick. The subject matter is well arranged and up to date and presented in a lucid, concise manner. This volume is recommended to those interested in this field.

L. J.

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FORTY YEARS OF PSYCHIATRY. NERVOUS AND MENTAL DISEASE MONOGRAPH SERIES NO. 57. By WILLIAM A. WHITE, A.M., M.D., Sc.D. Pp. 154. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1933. Price, $3.00.

REGARDING "insanity" as a purely social and legal term indicating a degree of maladjustment that requires special attention, the author undertakes to describe what has happened in its care during the forty years in which he has been actively concerned with it and to evaluate the gigantic progress that has been accomplished in this phase of man's understanding of man. Fortunately rich in autobiographical details—personalities furnishing to most of us more interesting reading than abstract ideas—the

book gives a wise mind's views on mental hygiene, psychoanalysis, medical psychology, mental hospitals administration, relations with the law and other problems that are now chiefly occupying this rejuvenated, active and most important of specialties. We heartily agree with his insufficiently appreciated view that "every physician ought to go into the community as well grounded in psychiatry as he is in the principles of obstetrics, pediatrics, surgery, and other medical specialties." E. K.

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BINOCULAR VISION AND THE MODERN TREATMENT OF SQUINT. By MARGARET DOBSON, M.D. (LOND.), Ophthalmic Surgeon to the New Sussex Hospital for Women and Children, Brighton; Oculist in Charge of the Kilburn (L. C. C.) Eye Clinic. Pp. 107; 32 illustrations. New York: Oxford University Press, 1933. Price, $2.75.

THIS small book aims to give the principles and practice of modern orthoptic training. The author considers that, as a result of exercise, the amblyopia of the squinting eye may be overcome, and in many cases by appropriate fusion training the squint may lessen or actually disappear.

The first three chapters deal largely with the author's ideas regarding the phorias and tropias. The last four are chiefly descriptions of instruments designed to carry out orthoptic training.

Many of the author's theories and practices will not be accepted by American ophthalmologists; but since there has been a constantly growing demand on the part of the public for information regarding "eye exercises," it may be well for physicians in this country to become acquainted with the methods used. It is unfortunate that treatments of this character lend themselves so readily to use by charlatans and honest but misguided doctors; there is, however, no doubt that some of the forms of exercises described are helpful adjuncts to our present methods of treatment. F. A.

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# BOOKS RECEIVED.

## NEW BOOKS.

*The Operative Story of Cleft Palate.* By GEORGE MORRIS DORRANCE, M.D., F.A.C.S., Professor of Maxillo-facial Surgery, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania; Surgeon to St. Agnes' Hospital, and to the American Oncologic Hospital, Philadelphia. Assisted by ENAYAT SHIRAZY, D.D.S. Pp. 564; 534 illustrations: Philadelphia: W. B. Saunders Company, 1933. Price, $6.50.

*Nosokomeion.* Quarterly Hospital Review No. 2, April, 1933, Containing the Proceeedings of the Third Hospital Congress. Pp. 441. Stuttgart: W. Kohlhammer, 1933.

*Nutrition.* Vol. X of Clio Medica. By GRAHAM LUSK, Sc.D., M.D., LL.D., Late Professor of Physiology, Cornell University Medical College, New York; Former Member, Royal Society; Corresponding Member, Preussische Akademie der Wissenschaften. Pp. 142; 13 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $1.50.

*The Medical Clinics of North America. Vol. 17, No. 1 (New York Number—July, 1933).* Pp. 324; 64 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price: Paper, $12; Cloth, $16.

*The Surgical Clinics of North America. Vol. 13, No. 3 (Lahey Clinic Number —June, 1933).* Pp. 275; 98 illustrations: Philadelphia: W. B. Saunders Company, 1933.

*The Nature of Disease Journal, Vol. II.* By J. E. R. McDonagh, F.R.C.S. Pp. 197. London: William Heinemann, Ltd., 1933. Price, 7s 6d, net.

*History and Source Book of Orthopaedic Surgery.* By Edgar M. Bick, M.A., M.D., Adjunct Orthopaedic Surgeon, Hospital for Joint Diseases, New York City; Adjunct Orthopaedic Surgeon, Montefiore Hospital, etc. Pp. 254; illustrated. New York: The Hospital for Joint Diseases, 1933. Price, $1.50.

*Histopathology of the Peripheral and Central Nervous Systems.* By George B. Hassin, M.D., Professor of Neurology, University of Illinois, College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Pp. 491; 229 illustrations. Baltimore: William Wood & Co., 1933. Price, $6.00.

*The Therapeutic Agents of the Quinoline Group.* By W. F. von Oettingen, M.D., Ph.D., Assistant Professor of Pharmacology, School of Medicine, Western Reserve University, Cleveland. Pp. 301. New York: The Chemical Catalog Co. Inc., 1933. Price, $6.00.

*The Doctrine of the Healing Power of Nature Throughout the Course of Time.* By Max Neuburger, M.D., Ph.D., Vienna. Translated by Linn J. Boyd, M.D., F.A.C.P., New York. Pp. 184. n.p., n.d. (New York, 1933).

*Frontiers of Medicine.* (A Century of Progress Series.) By Morris Fishbein, M.D., Editor, Journal of American Medical Association, and Hygeia, the Health Magazine. Pp. 207. Baltimore: The Williams & Wilkins Company, 1933. Price, $1.00.

*Sane Sex Life and Sane Sex Living.* By H. W. Long, M.D. With a Special Introduction by W. F. Robie, M.D. Pp. 151. New York: Eugenics Publishing Company, Inc., 1922. Price, $2.00.

*On Phasic Introductory and Release Effects of the Cocaine Group on Vessel Preparations and an Attempt at a General Appraisal of Phase Effects.* By Eduard Rentz, Riga. Translated and Abstracted by Linn J. Boyd, New York: n.p., n.d. (New York, 1933).

*Health and Environment.* (Recent Social Trends Monograph.) By Edgar Sydenstricker. Pp. 217; 50 illustrations. New York: McGraw-Hill Book Company, 1933. Price, $2.50.

## NEW EDITIONS.

*Manual of Veterinary Bacteriology.* By Raymond A. Kelser, D.V.M., A.M., Ph.D., Major, Veterinary Corps, United States Army; Officer in Charge, Veterinary Laboratory Division, Army Medical School, etc. Pp. 552; 93 illustrations and 11 tables. Second Edition. Baltimore: The Williams & Wilkins Company, 1933. Price, $5.50.

In the vast domain of veterinary bacteriology, so largely unexplored, a comprehensive treatise is still a practical impossibility. The present work, however, not only helps to fill a wide gap—there being only one other recent work on the subject in English—but presents in compact space a wealth of material that has been assiduously prepared and kept up to date. It should be indispensible to those engaged in most kinds of veterinary and public health work.

*The Biology of the Protozoa.* By Gary N. Calkins, Ph.D., Sc.D., Professor of Protozoölogy, Columbia University. Pp. 607; 223 illustrations, and 2 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $7.50.

# PROGRESS
OF
# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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**Idiopathic Hypochromic Anemia.**—WINTROBE and BEEBE (*Medicine*, 1933, **12**, 187) thoroughly discuss this so-called new type of anemia which has aroused considerable interest among hematologists the past 3 years. The report is based upon those cases which have appeared in the literature, together with a study of their own 25 cases. Ninety-six per cent of the patients have been women and 82 per cent were between the ages of 20 and 50 years, very few having had their menopause. The type is asthenic and a familial incidence is not unusual. In certain instances inadequate convalescence from pregnancy might be an initiating factor. The disease is always insidious in onset and may be expressed by a variety of subjective symptoms, none of which differs much from those which occur in any type of anemia. The physical examination is, however, quite characteristic. The waxy, bloodless appearance of the tired, apathetic woman, poorly constructed constitutionally, with papillary atrophy of the tongue and a certain number of instances with koilonychia, presents a rather typical picture. An almost constant observation is an absence of free hydrochloric acid and a low total acid with a marked deficiency of the hemoglobin, together with an invariable reduction in the size of the red cells. As a consequence the volume of packed red cells, the mean corpuscular volume and the mean corpuscular hemoglobin are all greatly reduced. There is no evidence of increased blood destruction. A striking feature is the magnificent response to iron therapy and the utter valuelessness of liver extract and desiccated hog stomach. The iron must be continued over a long period of time and in large doses. Bloomfield has doubted the authenticity of this syndrome and a number of writers have suggested that chlorosis and idiopathic hypochromic anemia are one and the same. The authors' answer to Bloomfield's objection is not entirely convincing, nor are they impressive in their dismissal of chlorosis as being a possible factor in the genesis of the condition. They suggest that the lack of free hydrochloric acid and low total acid may alone be the fundamental disorder in this type of anemia. Probably the best hypothesis, they indicate, to explain the pathogenesis of idiopathic hypochromic anemia is one of defective gastric secretion in an individual who loses blood, repeatedly at the menses or during pregnancy, who is unable properly to synthetize hemoglobin from the diet.

# SURGERY

UNDER THE CHARGE OF

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**The Symptoms Resulting From the Bite of Latrodectus Mactans.**—(See also article by J. WALSH and W. G. MORGAN on "Arachnidism; Report of a Series of 29 Cases of Poisoning from the Bite of the Latrodectus Mactans," in this issue.) A correct diagnosis in patients with acute abdominal symptoms is often difficult due to variations from the classical clinical picture of the various disease entities encountered. While exact diagnoses in this region are important, the most urgent decision which has to be made is whether or not the condition requires an immediate laparotomy. For this reason the symptom complexes of acute non-surgical abdominal conditions are of primary interest to the surgeon. A condition of this type results from the bite of the black spider, Latrodectus mactans. While the occurrence of arachnidism is undoubtedly rare in urban practice, the fact that within a period of a little over 1 year 6 such cases were treated in the University of Virginia, and 29 collected in the Walsh and Morgan series, indicates that in less thickly populated areas it is not a rare condition. Commenting on the 6 cases MORTON (*Arch. Surg.*, 1933, **26**, 64) points out that even without a history of the bite of a spider the diagnosis is not difficult if one keeps the possibility of the condition in mind, but that one may just as easily make the mistake of regarding the condition as a surgical one if not familiar with the signs and symptoms of the condition.

The patient may or may not be aware that he has been bitten and it may be difficult to find the wound, even by thorough inspection. All the patients reported by Morton had severe cramping pains and rigidity throughout the abdomen. Tenderness was not commensurate with the degree of rigidity, and in addition there was pain or aching in the muscles of the back and thigh. The pain usually starts in a few minutes to an hour. The temperature rises to about 99° and 100° F. The leukocytosis may reach 20,000, and the pulse rate and blood pressure elevated. Morphin may relieve the pain but not the rigidity. Nausea and vomiting are usually present.

The chief points of differentiation between arachnidism and an acute surgical abdominal lesion are the history of the spider bite, the generalization of the rigidity and pain, the difference between the degree of the tenderness and the rigidity, and the occurrence of pain in the back and sometimes in the legs.

The "black widow" or Latrodectus mactans is widely distributed throughout the United States but is more abundant in warmer sections of the country. Other cases reported within the last 2 years, in addition to Morton's, were described by CORNWELL (*Southern Med. and Surg.*, 1931, **93**, 885) and TOLLESON (*J. Med. Assn., Georgia*, 1933, **22**, 30).

These cases occurred in the South and were quite similar to those reported by Morton. BOGEN (*Arch. Int. Med.*, 1926, **38**, 623) reported 15 cases of arachnidism occurring in Los Angeles.

The reader is referred to the article by Walsh and Morgan in the present issue of this Journal for further details.

## THERAPEUTICS

UNDER THE CHARGE OF

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**The Serum Treatment of Scarlet Fever and Erysipelas.**—BAXTER (*Glasgow Med. J.*, 1932, **118**, 361) presents the results of 2 extensive clinical studies on the efficacy of concentrated scarlet fever streptococcic antitoxins for that disease and of various serums and antitoxins in the treatment of erysipelas. To test the scarlet antitoxin he employed one of two standard commercial sera in a series of 120 cases selected because of their severity. The serum was injected intramuscularly, generally in a dose of 10 cc. Seventy per cent of the patients received serum before the fourth day of illness, and in this group 66 per cent made excellent recovery, while 34 per cent developed some complication. In the group receiving serum after the fourth day approximately one-half recovered without complications. While the group is too small to give satisfactory data on the influence of the antitoxin on mortality, the author feels that it is reasonable to believe that the deaths in this severe group would have been greater without the use of serum. No ill-effects were observed in any instance. In some of the graver cases a second dose of the serum was required. An initial rise of temperature following the injection of serum developed within 8 hours in approximately 90 per cent of the cases, following which the temperature dropped steadily for the next 24 to 36 hours. The fall of temperature was delayed in the most severe cases and in those in which treatment was not begun until after the fourth day of illness. In almost every patient there was a pronounced improvement in the circulation following the use of serum, but the most extraordinary change observed was the prompt and almost constant disappearance of the symptoms of toxemia. The rash disappeared within 12 hours in three-quarters of the patients and there was rapid subsidence of the throat manifestations. The incidence of complications seemed to be significantly reduced, and the required period of hospitalization was markedly shortened in 60 per cent of the cases, although these patients were not dismissed from the hospital before the usual period of time had elapsed. Only 14 per cent of the patients showed serum disease which was generally of mild nature and only 1 patient showed

a true relapse. For the treatment of erysipelas the following sera were tried: A polyvalent antistreptococcic serum, scarlet fever antitoxin of 2 different manufacturers, erysipelas antitoxin and diphtheria antitoxin. Satisfactory results were secured with only 1 of the 5 sera, namely, the scarlet fever antitoxin of Burroughs and Wellcome, and the results from erysipelas antitoxin were notoriously unsatisfactory. Efforts to limit the spread of erysipelas by the intradermal injection of one or other of the sera around the lesion were unsatisfactory and the treatment proved too painful to justify its further trial. Intramuscular administration of the serum, in doses ranging from 10 to 30 cc. of the B. and W. scarlet fever antitoxin alone, were followed in the majority of cases by a critical fall of fever with subsidence of toxemia, although the local skin lesion continued to spread with diminished intensity in 30 per cent of the cases after the injection of serum. The most satisfactory results were secured from the intravenous injection of from 20 to 30 cc. of the scarlet fever antitoxin which produced a critical fall of temperature and elimination of evidences of toxemia in the great majority of cases, however severely ill. In 60 per cent of the cases so treated the skin lesion began to subside within 24 hours after the critical fall of temperature. Desquamation began within 48 hours of the crisis. There were frequent immediate serum reactions in the form of rise of temperature, pulse and respiration rate following within 1 hour after the intravenous use of serum among the earlier cases, but this was largely avoided in the later ones by previous skin testing, warming the serum to blood temperature and its very slow administration. The incidence of complications was very greatly lessened in the treated group as compared to a control untreated group. Complication appeared in only 5 of 73 cases treated intravenously and in none of 41 treated intramuscularly. These complications included 1 case of tonsillitis, 1 of adenitis and 3 of abscess formation, while in the control group 2 per cent were complicated by nephritis, 2 per cent by endocarditis, 4 per cent by pneumonia and 30 per cent by abscesses. The average duration of hospitalization in control cases was 28 days as compared to an average of 15 days for patients treated with scarlet fever antitoxin.

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**Some Investigations on Irradiated Ergosterol.**—In view of a number of conflicting opinions concerning the constitution, production, toxicity and therapeutic efficiency of crystalline vitamin $D_2$, WINDAUS and LÜTTRINGHAUS (*Deutsch. med. Wchnschr.*, 1932, **58**, 1669) present a discussion of some of their own recent investigations as well as those of other workers. These show that the irradiation of ergosterol is capable of producing its conversion into a group of substances which are known as lumisterin, tachysterin, vitamin $D_2$, suprasterin I, suprasterin II, and an impure mother substance known as No. 248. The authors find that crystalline vitamin $D_2$ can be produced in proportions representing about 50 per cent of the original ergosterol and that the particular method and wave length of irradiation is of no importance save that it has a slight quantitative influence upon the production of vitamin $D_2$. They find that vitamin $D_2$ represents at least 90 per cent

and probably actually all of the antirachitic potency of irradiated ergosterol. They also find that it is easily produced in crystalline form, in which form it is quite stable. The question having been raised as to whether the toxicity of irradiated ergosterol was due wholly to the contained vitamin D, or was in part due to the other substances known to be present, is discussed by the authors who show, by their investigations, that the toxic action is chiefly inherent in vitamin D. They conclude, therefore, that there is no nontoxic antirachitic vitamin. However, quantitative studies on toxicity show that the crystalline vitamin $D_2$ is considerably less toxic in proportion to its antirachitic potency than is the impure irradiated ergosterol. The greater toxicity of the impure preparation is due chiefly to its content of tachysterin which is, while toxic, devoid of antirachitic activity. Finally, they point out that the ability to produce a pure crystalline vitamin D renders it no longer necessary to resort to biologic methods of standardization for the establishment of an antirachitic dose, since 1 mg. of this crystalline product represents 40,000 international antirachitic units. It would seem from these investigations that the crystalline product possesses the therapeutic advantage of a more favorable relationship between antirachitic potency and toxicity than exists in the cruder irradiated ergosterol.

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**Changes in the Blood Following General Quartz Lamp Irradiation.**—The results of investigations on the effect of quartz lamp irradiation may be summarized as follows: (1) In healthy animals and man it is ineffective. (2) In experimentally induced anemias it aids hematopoiesis. (3) In human diseases the effect on red cell count and hemoglobin is conflicting. TEPLOFF and MESCHERITSKAJA (*Deutsch. Arch. f. klin. Med.*, 1932, **174**, 399) studied this problem more thoroughly, on 2 young dogs, 2 healthy persons and 7 patients (5 diabetics, 1 with diabetes insipidus and 1 with polyneuritis). The measurements of the urobilin content of urine and feces, as well as the red cell count, hemoglobin content and number of reticulocytes in the blood were performed during a 6- to 7-day control period, during 3 to 4 weeks of irradiation and during a period of 6 to 7 days after the irradiation. Under such conditions both in animals and in man there developed, as judged from the increased urobilin content of the feces, an increased hemolysis. Simultaneously, as judged from the increased reticulocyte count, there occurs increased erythropoiesis. The hemoglobin content and red cell count remain essentially unaltered, but the formation and destruction of the blood take place more rapidly. Simultaneously with, or soon after, the cessation of the medication both the hemolysis and the erythropoiesis become normal or subnormal.

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**The Action of Metaphyllin (Euphyllin) on Cheyne-Stokes Breathing and Asthma of Cardiovascular Origin.**—GUGGENHEIMER (*Ztschr. f. Kreislaufforsch.*, 1933, **25**, 98) finds metaphyllin administered intravenously in doses of 0.48 gm. in 10 cc. of distilled water or of 20 per cent glucose solution to be a most effective remedy for the control of Cheyne-Stokes breathing and of cardiac asthma. In cases where the evidences of cardiac failure are pronounced it is advantageous to add

0.25 mg. of strophanthin to the dose to increase the efficiency of the heart. From his personal studies and an analysis of the literature on the pathologic physiology of these two conditions supplemented by a consideration of the pharmacologic actions of metaphyllin, the author concludes that the drug accomplishes its effects by a direct dilatation both of the coronary arteries and of the arteries supplying the respiratory center, thus improving by both mechanisms the blood supply to the center. He points out that there is also evidence to justify the belief that metaphyllin also diminishes the bronchospasm which may be present in cardiac asthma. Finally, it seems evident that the action of the drug is unrelated to its content of ethylene diamin and that it depends in part upon the theophyllin and in part upon the action of the compound as a whole.

## PEDIATRICS

UNDER THE CHARGE OF

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**Chronic Non-specific Nephritis.**—ALDRICH and BOYLE (*J. Am. Med. Assn.*, 1933, **100**, 1979) give a brief description of the clinical features exhibited by 40 children with chronic non-specific nephritis along with the results of treatment over 10 years with low-protein diets. After the institution of high-protein diets with high-vitamin content and with improved hygienic care, definite improvements were seen. After critical consideration of the clinical picture and pathologic anatomy of this disease the authors questioned some of the generally accepted theories as to its pathogenesis. It was noted that only an occasional patient with chronic non-specific nephritis gave a history of acute postinfectious nephritis at the onset and that even the patients most severely ill with postinfectious nephritis usually made complete and permanent recoveries. It seemed possible that a pathologic process of a more benign nature than the progressive sclerosis found in chronic non-specific nephritis. They began to think of chronic nephritis as a separate entity clinically and attempted to differentiate it even in its earlier stages before the chronicity alone established its nature. They attempted to find some other cause than microbic infection. In looking about it was noted that the cases were found in the dispensaries, and that it was very rare in the well-to-do. The patients were malnourished and surrounded by poor hygienic environment. As the patients were retrogressing a radical change was decided upon. All of the preconceived ideas of diet were discarded, and the children were treated as another group of undernourished children would be. They were given meat or eggs 3 times a day. Salt was allowed to all those who were not definitely edematous. All known vitamins were included in the diet. In addition every effort was made to improve the hygiene. The results following the change were very rapidly noticeable. In general neither the blood pressure nor the blood non-protein nitrogen values increased

with the change. While the albuminuria persisted in most cases, it tended to decrease in amount, and disappeared entirely in 3 cases. As a result of 2 years experience with this dietary and hygienic régime the majority of the patients have shown definite clinical improvement.

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**Systolic Murmurs in Children.**—Bass, Mond, Messeloff and Oppenheimer (*J. Am. Med. Assn.*, 1933, **101**, 17) studied 64 children with systolic murmurs, both organic and functional. The records of all the murmurs contained vibrations of high frequency. Of the functional cases 86 per cent showed high-pitched vibrations only, while organic cases had low- as well as high-pitched vibrations. This suggests an additional means of differentiating between the two types of murmurs. In seeking the cause of the admixture of low vibrations in the organic cases, several factors must be considered. In the valvular organic murmurs, the murmur originates at the site of the valvular apparatus. In mitral insufficiency the high ventricular pressure forces a stream of blood back into the auricle through a more or less narrow opening caused by a shortening of the valvular leaflets and their consequent inability to close completely. The intensity of the murmur will depend on the velocity, the pressure and the volume of the backflow, which plays on the free edge of the valve as a bow on the strings of a violin. From this point the vibrations are transmitted to the whole system of auricle and ventricle. Similar considerations are applicable to the case of aortic stenosis when a high pressure stream strikes against a narrowed aortic ring during ventricular systole. These organic murmurs are usually louder than the functional type, which often appear as soft blows. This in itself is undoubtedly a factor that accounts partly for the low pitched vibrations. The louder the murmur the wider will be the area indirectly set into vibration and the greater the mass of tissue affected. Living tissues are at best not ideal conductors, and the original murmur is distorted by an admixture of widely varying vibrations. Occasional components of low frequency are demonstrable in rather soft organic murmurs, and on the other hand may be lacking in the occasionally quite loud systolic murmurs at the pulmonary area, which are universally regarded as functional. Therefore, some additional factor besides the intensity of the murmur must be assumed to account for the presence of low-pitched vibrations in organic valvular cases. The authors set forth a theory that, in cases of valvular lesions, the volume of blood set in direct vibration together with surrounding portions of the wall of the heart is relatively large and therefore gives ample occasion for the production of vibrations of low frequency, some of which may lie even below the acoustic range. It also gives a hint as to the explanation why the non-organic or functional murmurs lack low-pitched vibrations. They believe that the latter murmurs may be caused by purely local disturbances which set up vibrations of only a limited area of heart muscle, in the immediate vicinity of the whorl.

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**Thrombosis of the Dural Venous Sinuses in Infancy and Childhood.**—Byers and Hass (*Am. J. Dis. Child.*, 1933, **45**, 1161) present a series of 50 cases of sinus thrombosis, which they divide into two groups. A certain number of cases were attributed to infection. No etiology was assigned to the remainder. Those infants in whom thrombi of the

primary type developed had a number of characteristics in common. They were less than 30 months of age. They often suffered from acute nutritional disturbances. Dehydration consequent to vomiting and diarrhea was usually the only important physical finding. The thrombi, almost invariably during the first or second week of the disease, formed in the midportion of the superior longitudinal sinus and propagated so that stasis was produced and coagulation of the blood occurred in the tributary cerebral veins. The most important factors in determining the site of localization in the sinus were the anatomic features that favored slowing and eddying of the blood current and any disease that produced concentration of the blood and sluggish circulation. The clinical picture of primary thrombosis was very variable. The condition was rarely diagnosed. Symptoms referable to an intracranial lesion appeared only after the circulatory obstruction had produced pathologic changes in the meninges and cerebrum. Hemorrhages in the meninges and hemorrhagic necroses in the cerebral cortex did not always produce symptoms or suggestive physical findings. The development of convulsions during the course of an illness or even after recovery was of important diagnostic value. Symptoms of meningeal irritation or evidence of hemorrhage into the subarachnoid space were frequently overlooked. Several cases were diagnosed as encephalitis. Many patients with primary sinus thrombosis should survive, but certain sequelæ might be expected to follow. In some cases there would be no residual anatomic change. In others, there would follow organization, resorption and virtual disappearance of the thrombus with only a small amount of fibrous tissue to mark the site of the lesion. Hemosiderosis, cystic degeneration, gliosis, calcification and atrophy of portions of the brain might well be expected to occur in the weeks and months following the original disease. Canalized thrombi, fibrosis, hemosiderosis, partial obliteration of the subarachnoid space, subarachnoid cysts and groups of newly formed bloodvessels might eventually mark the sites of hemorrhages into the leptomeninges. Hydrocephalus might develop as the result of interference with the absorption of spinal fluid.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Subcutaneous Fat Necrosis of the Newborn.**—In an attempt to clarify the various types of subcutaneous induration occurring in newborn or young children, Fox (*Arch. Derm. and Syph.*, 1933, **27**, 237) divides the cases into four groups: (1) Adiponecrosis subcutanea neonatorum; (2) sclerema adiposum (sclerema neonatorum); (3)

sclerema edematosum (edema neonatorum), and (4) scleroderma. The first type of induration, subcutaneous fat necrosis of the newborn, is a self-limited, localized process affecting various-sized areas of the body, often in a fairly symmetrical manner. The lesions appear from 2 to 20 days after birth, appearing as deep-seated indurated areas varying in size from a split pea to lesions involving the greater part of the back and buttocks. The color at the outset is usually bluish-red, the skin returning to its normal color before the lesions have softened and disappeared. The most striking feature is the non-pitting induration of the subcutaneous tissue, which areas are fairly well defined and may or may not be movable on deeper parts. The lesions disappear completely in from 5 weeks to 5 months, only rarely leaving slight traces of atrophy in their wake. The general health of the infant remains undisturbed throughout the evolution of the process. Pathologically the process is essentially a necrosis of fat cells and an infiltration of epithelioid and giant cells. The most important etiologic cause is probably some form of trauma, as compression during birth and too vigorous methods of resuscitation. Sclerema adiposum (sclerema neonatorum) in contrast is seen chiefly in undernourished, debilitated and premature infants. It begins as an edematous swelling of the feet extending upward. Some cases are extensive while others involve only localized areas, all showing a characteristic pitting on pressure. The disease is usually fatal in from 4 to 5 days. Scleroderma of the newborn is an exceedingly rare disease and the diagnosis is only justified if the indurative process remains unchanged for a year or more. The author presents 5 case reports of subcutaneous fat necrosis with histologic study in 3.

**Skin Changes in Chronic Encephalitis.**—An attempt is made by HAXTHAUSEN (*Acta Dermat.-Vener.*, 1932, **8**, 408) to collect the various dermatologic accompaniments of chronic encephalitic states. The best known is a pronounced seborrhea, most conspicuous on the face, which looks as if it were smeared with grease. It is supposed that this is caused by a condition of irritation in the assumed vegetative centers of sebum secretion. Anomalies of pigmentation are also common, especially what has been termed "brown forehead ring." The author has also seen this lesion in other affections of the central nervous system. It resembles chloasma uterinum, but in its typical form is an arched band of hyperpigmentation 1 cm. broad situated on the forehead with the summit of the arch near the hair line and the ends fairly straight at the temples. Some cases show a more diffuse pigmentation over the face with free white islands of various sizes. Several unusual expressions of eczematoid dermatitis have been observed. The lesions are for the most part unilateral eczematoid patches with pseudosegmental distribution, fairly defined outlines often running in straight lines, all suggestive of a relationship to central vegetative centers. The author maintains that self-inflicted lesions of the skin (pathomimia of Rasch) are conspicuously common in chronic encephalitis, 5 cases being observed in a group of 50 such patients studied. It is probably another expression of changes of character seen among such patients. Several isolated examples of trophic lesions of the skin and a bizarre hypertrichosis of the crura were also observed.

# GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**The Supports of the Uterus.**—As a result of his studies of the gross and microscopic appearances of the paravaginal and parametrial tissues, KOSTER (*Am. J. Obst. and Gynec.*, 1933, **25**, 67) concludes that there is no ligamentous tissue, which might by its presence be able to support the uterus, to be found in the base of the broad ligament. Such a structure is described in textbooks under the name of Mackenrodt's ligament, the cardinal ligament, the uteropelvic ligament or the infundibulopelvic ligament, and is supposed to be around or near the uterine vessels extending from the uterus out to the lateral pelvic wall. He states that the name ligament attached to any structure existing in the base of the broad ligament is a misnomer and is distinctly misleading. The uterus cannot depend for support on any structure to be found in the base of the broad ligament, running from the cervix out to the lateral pelvic wall, any more than it can on any of the tissues to which it is attached. From this statement it can be seen that the explanation of the development of prolapse and its cure, can no longer include a consideration of these so-called ligaments so that operations for the cure of prolapse of the uterus based upon shortening of such non-existing structures have no rational basis. No doubt those gynecologists who have been partial to such operations will be in violent opposition to the above statement, but it all boils down to what should be considered a ligament. No one questions the existence of areolar connective tissue in the parametrial tissues but the existence of true tough fibrous tissue such as is usually associated with the word ligament is indeed very doubtful.

**Pelvic Sympathectomy.**—Although the profession in this country has not shown much interest in pelvic sympathectomy it has frequently been performed in some European clinics. COTTE (*Zentralbl. f. Gynec.*, 1933, **57**, 72, 77), of Lyon, has resected the presacral nerve in over 200 cases with results that appear to be very satisfactory. The operation is indicated for the relief of severe pelvic pain such as is experienced in the late stages of cancer of the cervix and also in the severe pain associated with functional dysmenorrhea which does not respond to the usual remedies. In this series the operation was performed for the relief of dysmenorrhea in 125 cases. The operation gave relief in severe cases of vaginismus and dyspareunia and seems to be of value in the treatment of various vasomotor diseases of the pelvic organs which are associated with leukorrhea and nervous hydrorrhea. He has never had any bad results which could be attributed to the operation such as bladder disturbances, menstrual difficulties, secondary trophic

changes in the vagina or vulva or atrophy of any of the genital organs. Since his first operation was performed more than 7 years ago, sufficient time has elapsed for any bad effects to appear. In 30 cases the patients have gone through pregnancy since operation without any complications and in no instance has an ectopic pregnancy occurred. To the gynecologist who intends performing this operation it is important to remember that the presacral nerve is not a single nerve but is in reality a sympathetic plexus, and in order to obtain the expected results all of the fibers of the plexus must be interrupted. This, however, is not difficult to accomplish if the technique described by the author is accurately followed.

## OPHTHALMOLOGY

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**Changes of the Optic Nerve Resulting From Pressure or Arteriosclerotic Internal Carotid Arteries.**—SAPHIR (*Am. J. Ophthal.*, 1933, **16**, 110) reports the results of gross and microscopic studies of the optic nerves obtained at necropsy from 6 patients with marked sclerosis of the internal carotid arteries. In 4 an aneurysmal dilatation was present in 1 of the carotids. None of the patients had shown any clinical evidence of loss of vision. Grossly, the optic nerves showed in all cases distinct flattening, thinning and compression, especially in the portion between the carotids and the membranous optic canals. The aneurysms produced also actual medial displacement of the nerves. Hyperemia of the small veins in the superficial portions of the nerves was seen in some cases and also definite impressions from the aneurysms. Histologically, however, the changes in the nerves were relatively mild. The glial and connective tissue fibers were usually moderately increased. In some instances the central bundles of the nerve seemed to be compressed and smaller than normal. Any degeneration present was more pronounced in the central than in the peripheral bundles. A slight perivascular lymphocytic infiltration was found only occasionally. Reduction of the size of the nerve seemed to have occurred in the main without appreciable degeneration, but with occasional myelin sheath degeneration in the central bundles. The chiasmal and intraorbital portions of the nerves were found to be normal. The arterioles within the optic nerves were normal and the gross changes present seemed to be due entirely to the effects of direct compression and not to nutritional disturbances. What histologic changes were present would suggest the possibility of central rather than nasal hemianopic field disturbances. From his observations in these cases, the author doubts that visual disturbances in old persons should often be assumed to be due to pressure on the nerves by sclerosed internal carotid arteries.

**The Results of Own Blood Injections Into the Anterior Chamber in Tuberculosis of the Anterior Segment of the Globe.**—SCHIECK (*Klin. Monatsbl. f. Augenh.*, 1933, **90**, 1) reports excellent results in the treatment of 14 cases of tuberculous iritis and iridocyclitis from the use of injections of the patients' own whole blood into the anterior chamber. The aqueous is withdrawn by means of a cannula and enough blood is injected to cover the surface of the iris and the pupil but not to fill the chamber completely. The patient is kept sitting up after the operation so that the blood settles into the lower part of the chamber and does not stay too long in contact with the lens capsule. So far, no untoward effect of the injections has been noted. Rise of tension has not occurred and no permanent clouding of the lens capsule has been noted. The effects have been uniformly good. The regression of the inflammation has been rapid, and so far there have been no recurrences in any of the patients treated by this method, an unusual course for tuberculous iridocyclitis in which recurrences are the rule. The patients all had positive tuberculin reactions and were treated with tuberculin also. The author thinks that the resistance of tuberculous iridocyclitis to ordinary methods of treatment is explained by the fact that none of the protective mechanisms of the blood are present in the aqueous. Patients with tuberculosis of the anterior segment of the eye are usually otherwise healthy and show no signs of tuberculosis elsewhere. Their blood must, therefore, contain adequate protective substances which are placed in contact with the diseased tissues when blood is substituted for aqueous in the anterior chamber. Injections of whole blood into the anterior chamber had no effect on a case of traumatic iridocyclitis, on a case of sympathetic ophthalmia, nor on 2 cases of tuberculous keratitis.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**Dynamics of Nasal Respiration.**—In seeking data concerning the physiology of nasal obstruction, KRIMSKY (*Arch. Otolaryngol.*, 1932, **16**, 705) concluded that for its interpretation one is obliged to form one's own deductions about a condition that should convey a more definite picture than is offered at the present time; and that, consequently, the the term "nasal obstruction," like "rheumatism," has become a frequent but loose expression to denote mild or severe degrees of nasal closure, and in a number of instances a mere subjective state not supported by clinical observation. The author believes, moreover, that "by creating an issue as to the importance of an intelligent approach to this important problem, much may be done to arrive at more definite indications for nasal surgical treatment for this condition, which in the present state of investigation cannot always stand the test of critical analysis. Two U gauges were required for the rhinometric tests—one containing water, for recording low pressures; the other containing mercury, for

forced pressure readings. Minutiæ of technique and an outline of recording are presented. From the information obtained from observations made on 8 human subjects, such conclusions are reached as: (1) the dynamics of nasal function offers a vast field for clinico-physiologic research; (2) the rhinometric test is essentially differential; (3) a disturbance in the equilibrium of nasal pressures points to a mild or severe degree of nasal obstruction, depending on the extent of the changes in the natural and forced pressures, respectively; (4) a progressive nasal obstruction first affects the natural pressures, then the forced inspiratory pressures and, lastly, the forced expiratory pressure; (5) nasal obstruction, though not uncommon, is far less frequent than ordinarily suspected; (6) while a marked drop in the forced pressure points to nasal obstruction, one should bear in mind that asthenic states and pulmonary disease, such as emphysema, may render it impossible for the patient to generate a greater force; in these cases, too, the differential changes should guide one in determining the nasal condition; (7) oral records were not helpful in arriving at these conclusions and, finally, while pressure tests are too time-consuming to be advocated as a routine procedure, they have value under several circumstances, which the author tabulates.

## RADIOLOGY

UNDER THE CHARGE OF

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**Studies of the Effect of Irradiation on the Healing of Wounds.**—POHLE and RITCHIE (*Radiology*, 1933, **20**, 102) exposed 78 rats to Roentgen rays (100 KV, 2 mm. of Al) immediately, 24 hours and 48 hours following incisions in the skin of the back. Half of each wound was irradiated following the cutting and the other half was protected. Sections were made of specimens taken at daily intervals from 1 to 9 days after incision. Delay in healing was most constantly observed in wounds treated 24 hours after cutting. Histologically this became evident from 3 to 4 days after the cutting, but seemed most apparent after about 7 or 8 days. The irradiation seems to have less effect on the epithelium than on the underlying connective tissue.

**Diagnosis of Uterine and Tubal Pathology Using Lipiodol.**—HARRIS (*Radiology*, 1933, **20**, 146), discussing the elementary features of uterosalpingography, regards it as an unrivalled means of establishing the diagnosis of uterine fibromyomas and pregnancy, and for determining the cause of sterility. When depicted by lipiodol the normal uterine shadow is triangular and the tubes appear as thin wavy lines extending to a widened ampulla. Occlusion of one or both tubes is often found

in cases of sterility. Intramural fibromas project into and deform the uterine shadow. Diagnosis of pregnancy, according to the author, can be made as early as 2 weeks after impregnation. The contour of the uterine triangle is deformed by the projection of the ovum, and both tubes are occluded. Although it is held that uterosalpingography is likely to cause abortion, the author feels that this will not often ensue if the introduction of the oil is stopped as soon as the patient complains of cramps.

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**The Roentgen Ray Evaluation of Breast Symptoms.**—It is held by LOCKWOOD (*Am. J. Roent. and Rad. Ther.*, 1933, **29**, 145) that the Roentgen examination of the breasts offers a high degree of accuracy in the diagnosis of cancer and other diseases. It is not offered as a substitute for other methods but as a valuable addition to them. In roentgenograms of chronic cystic mastitis the small cysts appear as clear areas 1 to 4 mm. in diameter; large cysts of the blue dome variety appear as large irregular clear spaces in the parenchyma. Cancer shows as a rather dense, irregular tumor often with a feathery periphery. The cancerous lymph node in the axilla is seen as a smooth, rather dense opaque area, whereas the inflammatory node is faint and irregular in outline.

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## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**A General Symptom in Brain Tumor.**—KLINKE (*München. med. Wchnschr.*, 1931, **77**, 50) presents 4 cases of cerebral tumor in which Kehrer's two signs were demonstrable in unmistakable fashion. The first of these comprises the production of pain on deep pressure over the back of the neck, a little to one side of the mid-line, at the site of emergence of the great occipital nerve. Associated pain reactions consist in flushing of the face, and flexion of the head and neck backward and to the homolateral side. Kehrer's other sign consists of pain on deep pressure over the points of emergence of the three branches of the trigeminal nerve on the face. While this maneuver may cause pain on one side only, or perhaps merely in one or two of the branches in cases of tic douloureux and of migraine, in patients with cerebral tumor all six points are painful on pressure. The author believes that these are early and valuable signs of increased intracranial tension analogous to the demonstration of papilledema. He states that further research is required to determine which of the two signs can be elicited first and whether there is any correlation between priority of appearance and site of the neoplasm.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**Cholesterin Content of Skin of Fetus and of Child in Relation to Solar Irradiation.**—ROFFO (*J. de phys. et de path. gén.*, 1932, **30**, 345) summarizes results of previous communications which indicate that cholesterin content of skin varies according to exposure to sunlight, regions freely exposed showing an increase, those kept in darkness a comparative diminution. The author now reports on determinations of cholesterin content of skin of fetus and young child. The cholesterin in skin of two regions—cheek and abdomen—was calculated. The average increase of cholesterin in skin of cheek of fetus compared with that of abdomen was 0.005 as compared with 0.07 in the infant of from 3 days to 3 years and 0.72 in the adult man. Moreover, skin of face of fetus and of child contains 1.24 times as much cholesterin as that of abdomen, that of adult man 3.53 times as much; or, if the increase be considered in percentage, the increase in the fetus is only 25 per cent and that of the child 39 per cent as compared with 253 per cent in the adult man. The slight difference of the proportions in the skin of the two regions in the fetus is attributed to the absence of solar irradiation during intrauterine life. The differences of cholesterin content of the skin in woman approach those of the child owing to protection given her skin. The cholesterin content of skin of forehead —a covered region of the face—is comparable to that of the abdomen. If the average of the figures for these two regions, especially in the skin of woman, is taken, the differential figures are slight, and close to those of the child and fetus. The author concludes that there is an increase of cholesterin in the skin of uncovered regions which is in proportion to age, and that this phenomenon is connected with the condensing action produced by the rays of the sun.

**Human Experiments with Brucella Abortus.**—In 1912 a review appeared in this Journal under the heading Infectious Abortion and its Relation to Man which suggested that the organism producing abortion in cattle might be capable of infecting man. Since then the human cases of infection with bacteria of this group have been frequently recognized, but whether the causative organism is the unchanged abortus bacillus discovered in 1897; a strain of B. melitensis (1889) of unusual distribution; or a race which passing through swine from cattle has adapted itself to the pig and incidentally has become more virulent for man as believed probable by THEOBALD SMITH (*J. Prev. Med.*, 1928, **2**, 345) is still unsettled. Immunologic methods have indicated a close relationship for members of this group

but have not been helpful in discovering changes in virulence of these bacterial by passage through different hosts. Brucella abortus has been active in dairy herds since 1893, according to the evidence of Theobald Smith, but the reason for the increasing incidence of human infections is still puzzling. Human experiments on 40 volunteers were undertaken in Puerto Rico by MORALES-OTERO (*P. R. J. Pub. Health and Trop. Med.*, 1930, **6**, 3) the various strains of the organs being given by mouth and through abraded and normal skin. Infections were established by both the mouth and the abraded skin. He was greatly impressed with the virulence of the porcine strains in man and with their ability to invade the gastro-intestinal canal in contrast to the inability of bovine strains to do so. In a later study (*J. Inf. Dis.*, 1933, **52**, 54) he obtained further evidence that the strains of bovine origin are of low pathogenicity for man since 3 volunteers after ingesting infected milk for 6 weeks showed no symptoms nor other evidence of infection, nor in 2 other volunteers did the Brucella abortus cause an infection *via* the skin. This method of approach to a confused and intricate problem deserves attention despite the obvious difficulties involved in such studies.

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**Infection of Accessory Sinuses in Vitamin A Deficiency: The Rôle of Carotene in Infection of the Upper Respiratory Tract.**—The important rôle of vitamin A in the prevention of infection, especially of the upper respiratory tract, upper digestive tract, nasal cavities and middle ear, is demonstrated by TURNER and LOEW (*J. Inf. Dis.*, 1933, **52**, 102) Carotene is the plant source of vitamin A and is relatively unstable, being converted to achrocarotene with loss of color and potency. Using olive oil as a solvent promotes absorption from the intestine, and the addition of hydroquinone or quinhydrone stabalizes the solution for as long as 4 months. The effect of carotene on growth and general health is shown by an experiment on rats. One hundred albino rats were reduced to a xerophthalmic state by giving a vitamin-A-free diet and were divided into 4 groups for treatment. Group A, those receiving active carotene for the test period of 35 days, showed an average gain of 39 grams with cure of xerophthalmia. At autopsy the animals appeared healthy, showed few systemic conditions, and a small number of suppurative conditions of the nasal cavities and middle ear. Group B, those receiving weak or faded carotene, showed a loss of 69 grams in weight with only slight improvement in xerophthalmia. Autopsy revealed evidence of vitamin A deficiency and 100 per cent of positive cultures from the nasal apertures. Group C were negative controls, receiving only olive oil. These showed loss of weight and severe xerophthalmia. The animals were poorly nourished and showed 59 per cent systemic conditions. Group D were positive controls, receiving cod-liver oil, appearing healthy and with no signs of suppurative or systemic conditions at autopsy. The flora obtained from the nasal and aural conditions were staphylococci, colon bacilli, a Friedländer-like bacillus and Micrococcus catarrhalis. The carotene therapy reduces the number of spontaneous suppurative lesions of upper respiratory tract occurring in animals deprived of vitamin A. Xerophthalmia was cured in 100 per cent and normal health regained in 74 per cent.

## HYGIENE AND PUBLIC HEALTH

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**A Ten-year Study of Toxin-antitoxin Mixture and the Schick Test in the Control of Institutional Diphtheria.**—YOUNG and CUMMINGS (*Am. J. Pub. Health*, 1932, **22**, 1151) conclude from their studies that true or subclinical diphtheria may be a factor in maintaining a high degree of institutional immunity to the disease. The span of artificially produced immunity as measured by the Schick test approximates 7 years, immunized positives returning rapidly to the positive state in the following years. Natural or Schick negative reactors tend to return to the positive state with the elimination of the influence of true or subclinical diphtheria. Administration procedure should include Schick surveys on immunized groups coinciding with the decline in the general level of immunity. Schick surveys at intervals beyond the one over which the protection against diphtheria may be assumed should include original natural negative reactors as well as artificially immunized negative reactors.

**The Infection of Cows With B. Abortus Variety of Brucella From a Public Health Standpoint.**—WILCOX (*Am. J. Pub. Health*, 1932, **22**, 1157) states that the milk of cows infected with the bovine variety of B. abortus is a potential source of infection for man. The danger of infection is relatively small when milk contaminated with the bovine variety is considerably diluted. Brucella agglutinins may be present in the blood of man due to the consumption of milk containing B. abortus. These antibodies may occur in the absence of clinical symptoms. Cows in whom abortions have occurred may develop immunity so that they calve normally and still continue to excrete B. abortus in their milk.

**Diet, Nutrition and Infection.**—HESS (*New England J. Med.*, 1932, **207**, 637) states that the antirachitic factor, whether given as ultraviolet irradiation, as irradiated ergosterol or as cod-liver oil, does not increase the immunity of infants to respiratory infections. Respiratory infections are not due to a lack of vitamin A and generally cannot be lessened by giving a diet rich in this factor even when supplemented with cod-liver oil. The average infant seems to receive an adequate amount of vitamin A in its milk, judging by the fact that xerosis of the eyes is exceedingly rare, and that no gain in weight or increase in immunity is brought about by adding vitamin to the diet. The same

seems to hold true for older children and adults, in view of the infrequency of night blindness, the first sign of this deficiency. A lack of vitamin C may induce heightened susceptibility to infection of the respiratory tract. It may, however, induce merely local susceptibility without appreciable loss of systemic immunity. This peculiar phenomenon is manifested by the occurrence of typical nasal diphtheria, associated with virulent diphtheria bacilli, but a Schick reaction negative to highly potent solutions of toxin.

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**A Study of the Dissociation of the Rawlins Strain of Bacterium Typhosum With Special Reference to Its Use in the Production of Antityphoid Vaccine.**—GRINNELL (*J. Exp. Med.*, 1932, **56**, 907) studied subcultures of the Rawlins strain of Bacterium typhosus used by 12 different laboratories for vaccine production and found that they all differed from recently isolated smooth strains in cultural characteristics, virulence and protective efficiency. Eleven of these Rawlins cultures gave both the flagellar and the somatic type of agglutination in antismooth rabbit serum, and the 1 culture so tested produced both flagellar and somatic agglutinins when injected into rabbits and man. Agglutination of neither the flagellar nor the somatic type can, therefore, be used as a test of the smoothness of a culture or as an index of immunity. Since the Rawlins strain differs from the smooth phase of Bacterium typhosus in cultural characteristics and in virulence, and is much less efficient than smooth strains as a protective antigen; and since the selection and maintenance of smooth cultures suitable for vaccine production present no serious difficulty, it would seem but logical to substitute virulent, smooth cultures for the very old Rawlins strain, if we are to expect the maximum protection from antityphoid vaccination.

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**The Maternal Transmission of Vaccinial Immunity in Swine.**—NELSON (*J. Exp. Med.*, 1932, **56**, 835) found that the introduction of vaccinia virus into the skin of swine calls forth a typical vesicular reaction which may be followed by a solid immunity. This acquired state of resistance was utilized in determining the route of immunity transmission from sow to young. The suckling young of immune sows, vaccinated on the 7th day or earlier, showed no reaction to the virus. Their hand-fed litter mates, however, were susceptible and reacted with the formation of vesicles. These observations indicate that the porcine placenta is largely impermeable to protective substances and establish the fact that colostrum functions as the vehicle for their transmission as it does for antibodies.

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**The Rôle of Activated Milk in the Anti-rickets Campaign.**—HESS (*Am. J. Pub. Health*, 1932, **22**, 1215) states that activated milk, in the fluid or dry form, possesses the advantage not only of providing an automatic method of preventing rickets and of supplying this essential factor in a medium rich in phosphorus and calcium, but, as has been shown, it accomplishes this end by means of an exceptionally small amount of the antirachitic factor. In view of these important advantages the author recommends the general use of such milk for infants and children, especially in large communities. Whether adults, whose

bones are growing at a much slower rate, require a supplement of vitamin D to their dietary must be left undecided, to be answered according to the outcome of subsequent investigation. There can be little doubt, however, that the rapidly growing organism requires this factor and that, in the temperate zones, the infant and child do not receive the optimal amount from the radiations of the sun and from the meager supply in the food.

**The Attenuation of Measles.**—STEWART (*New England J. Med.*, 1932, **207**, 780) believes that under conditions of private practice it is well worth while to protect the brothers and sisters of a child with measles by intramuscular injections of blood from some older member of the family who has had measles. This is especially true of the younger children. Unless a child is already seriously ill, it is wisest to attempt to produce an attenuated form of the disease, which presumably gives lasting immunity. Twenty cubic centimeters of whole blood can easily be injected without delay or complicated equipment. The history that a child has had measles should not be too thoroughly relied upon.

**Pasteurization of Milk Artificially Infected With Two Strains of Brucella Suis.**—PARK, *et al.* (*J. Bacteriol.*, 1932, **24**, 461), found 2 strains of Brucella suis, in hermetically sealed glass tubes of whole milk (500,000,000 organisms per cc.), to be non-viable after 20 minutes at 140° F., after 15 minutes at 142° F., and after 7 minutes at 144° F. The same strains proved more resistant to heat in cotton-stoppered tubes of milk. Brucella suis survived for 30 minutes at 144° F. in milk containing 10,000,000 to 500,000,000 organisms per cc., but the same period of time at the same temperature destroyed Brucella suis in milk containing 5000 to 1,000,000 organisms per cc. Therefore, it appears that the thermal death time is influenced by the degree of contamination. The data suggest that efficient pasteurization will prevent milk-borne porcine brucelliasis. However, final conclusions are withheld pending results of studies on commercial pasteurizers.

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